SCHEDULE-CONTROLLED MATCHING-TO-SAMPLE IN THE PIGEON: DISRUPTION OF PERFORMANCE BY CHLORDIAZEPOXIDE AND METHOCARBAMOL

BY

STEVEN IRA DWORKIN

A DISSERTATION PRESENTED TO THE GRADUATE COUNCIL
OF THE UNIVERSITY OF FLORIDA IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1981

To my parents, Bess and Henry Dworkin.

ACKNOWLEDGMENTS

I would like to take this opportunity to formally thank Marc N. Branch for helping to make my graduate training both thorough and enjoyable. His friendship, encouragement and academic advice have resulted in my understanding of and appreciation for the experimental analysis of behavior and behavioral pharmacology.

My supervisory committee, Marc Branch, E.F. Malagodi, H.S. Pennypacker, Robert Waldbillig and Steven Childers, deserves some of the credit for getting this dissertation into its present form. I also thank them for the formal and informal interactions I received from them during my training.

I believe that a significant proportion of a graduate student's training is a direct result of interactions with his or her peers. I therefore thank Greg Galbicka, Tim Bartness, Ron Allen, Anne Sicignano, Kate Saunders, Dean Williams, and Glen Sizemore for countless hours of stimulating conversations.

Words cannot express the full appreciation I have for my parents Bess and Henry Dworkin. Without their continuous support this goal would have never been reached. I also thank Susan and Barry Frieman for their many words of encouragement over the years.

Finally, Serene Mirkis should be acknowledged for putting up with me during some very demanding times. She is also responsible for keeping me on a straight and broad path of a science of behavior.

TABLE OF CONTENTS

		PAGE
ACKNOWLEDGMENTS		iii
LIST OF TABLES		vi
LIST OF FIGURES		vii
ABSTRACT		viii
CHAPTER		
I	BACKGROUND	1
II	INTRODUCTION	15
III	METHOD	18
	Subjects	18
	Apparatus	18
	Procedure	19
	Drug Procedure	20
	Analysis of Results	23
IV	RESULTS	26
	Control Performance	26
	Acute Effects of Chlordiazepoxide	31
	Effects of the Daily Injection of 17.0 Mg/Kg.	40
	Dose Effects of Chlordiazepoxide and Saline During Chronic Chlordiazepoxide Administration	48
	Post-Chronic Effects of Chlordiazepoxide	51
	Acute Effects of Methocarbamol	51
V	DISCUSSION	57
LIST OF APPENDICES		65
APPENDIX		
A	RAW DATA OF NUMBER OF CORRECT AND INCORRECT RESPONSES ON FOUR TYPES OF TRIALS	66

PAGE

B PAUSE AND RUN TIMES FOR BOTH COMPONENTS. 73

C SOFTWARE PROGRAM--SKED STATE TABLE 76

REFERENCE NOTES 81

REFERENCES. 82

BIOGRAPHICAL SKETCH 94

LIST OF TABLES

TABLE		PAGE
1	List of Procedures and Number of Sessions Each Was Studied Before Chlordiazepoxide Administration. . .	21
2	Order of Drug Procedures and Number of Sessions Studied	24
3	The Effects of Chlordiazepoxide on the Index of Curvature During Both Acute and Chronic Administration.	35
4	Post-Chronic Effects of Chlordiazepoxide on Response Rates and Accuracy.	52
5	Acute Effects of Intramuscular and Oral Administration of Methocarbamol on Response Rates and Accuracy . .	54

LIST OF FIGURES

FIGURE		PAGE
1	Cumulative response records of control performance and drug effects under the mult FI 5 min FR 5 schedule of matching-to-sample.	28
2	Number of correct and incorrect side-key responses during successive 30-sec segments of the FI schedule.	30
3	Effects of chlordiazepoxide on accuracy and rates of responding during the two schedule components for both subjects	33
4	Effects of chlordiazepoxide on the number of correct and incorrect responses in tenths of the interval .	37
5	Effects of chlordiazepoxide on accuracy under both schedule components	39
6	Cumulative records from the first four consecutive injections during the chronic administration of 17.0 mg/kg chlordiazepoxide	42
7	Daily values of index of curvature during the FI and accuracy during the FR and FI when 17.0 mg/kg was administered daily.	44
8	Accuracy of the four types of trails during the daily administration of chlordiazepoxide.	47
9	Effects of chlordiazepoxide on overall response rates, correct rates and accuracy during acute drug administration or during daily administration of 17.0 mg/kg chlordiazepoxide	50
10	Cumulative records of responding during control sessions and sessions preceded by the oral administration of methocarbamol	56

Abstract of Dissertation Presented to the Graduate Council of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SCHEDULE-CONTROLLED MATCHING-TO-SAMPLE IN THE PIGEON: DISRUPTION OF PERFORMANCE BY CHLORDIAZEPOXIDE AND METHOCARBAMOL

By

Steven Ira Dworkin

August 1981

Chairperson: Marc N. Branch
Major Department: Psychology

The effects of chlordiazepoxide and methocarbamol on schedule-controlled behavior of pigeons were studied. Keypecking was maintained using a conditional discrimination (matching-to-sample) procedure under a multiple schedule of intermittent food presentation. In this procedure, a peck on a center key darkened the key and illuminated two side keys. A response on one of the side keys darkened both side keys and the center key was again illuminated. After 5 min the first response to the side key that was the same hue as the center key on that trial (correct response) resulted in food presentation (Fixed Interval 5 min). Two overhead lights were then illuminated and the fifth correct response resulted in grain presentation (Fixed Ratio 5). The fixed-interval and fixed-ratio schedule then alternated through the session.

Acutely, low doses of chlordiazepoxide produced significant decreases in response accuracy during the fixed-interval component with one subject (2122) and during both schedule components with the other subject (2155). Overall response rates, however, were slightly increased in either the FI component (2122) or both components (2155), while the rate of correct responses was generally unaffected. Increasing the dose of chlordiazepoxide resulted in dose-related decreases of correct and overall response rates and accuracy in fixed-interval and fixed-ratio components for both subjects.

Daily administration of 17.0 mg/kg of chlordiazepoxide resulted in rapid tolerance to the rate-decreasing effects of the drug for both subjects. Tolerance to the accuracy-reducing effects took considerably longer to develop with subject 2122 and was not observed with subject 2155. The sensitivity of response accuracy and response rates to disruption by the acute administration of the drug was corrected with the differential development of tolerance for these two measures.

Methocarbamol, a drug that has muscle-relaxant effects but does not produce sedation, resulted in decreased rates of responding but did not affect accuracy, suggesting that the effect of chlordiazepoxide on response accuracy was not related to its muscle-relaxant properties.

CHAPTER I
BACKGROUND

Since the synthesis of chlordiazepoxide in the late 1950's, the benzodiazepines have become the most widely used of all drugs (Lader, 1980). Although there are several differences among the more than 100 tested compounds included in this class of drug, several of their behavioral effects are similar (cf. Harvey, 1980; Lader, 1980). Benzodiazepines have been demonstrated to have anticonvulsant, muscle-relaxant, and sedative-hypnotic properties. It has also been demonstrated that these drugs have reinforcing properties and can maintain responding that leads to their administration in nonhuman as well as human primates (Griffiths et al., 1976, 1979; Griffiths et al., 1980). Benzodiazepines are most frequently prescribed for their sedative properties and in the treatment of "anxiety." In fact, two such drugs, chlordiazepoxide and diazepam, account for 75% of the 100 million yearly prescriptions for all sedatives in the United States (Baldessarini, 1980). It has also been estimated that one in 10 adult males and one in five adult females in the United States and Europe use prescription tranquilizers at least once a year (Lader, 1980).

Over the past 20 years, a large number of studies on the pharmacological characteristics and the behavioral effects of the benzodiazepines have been reported, and the past four years have brought about significant advances with respect to understanding the biochemical and pharmacological mechanisms of these drugs. In light of these recent reports,

the present status of the benzodiazepines in psychopharmacology resembles that of the opiate narcotics (cf. Snyder and Childers, 1979) just a few years ago. As with the opiates, highly specific binding sites for benzodiazepines have been located in mammalian brain (Braestrup and Nielsen, 1980; Lippa et al., 1978; McCarthy and Harden, 1981). The affinity of different benzodiazepines for these binding sites has been shown to be related to their clinical potency (Squires and Braestrup, 1977; Lippa et al., 1978; Robertson, 1979). Furthermore, several endogenous ligands for the benzodiazepine receptor have been suggested (cf. Marangos et al., 1979; L. Iversen, 1980). However, none of these compounds shows high affinity binding and therefore cannot be designated as an "endogenous benzodiazepine." Further complicating the analysis is the fact that a benzodiazepine antagonist has not been found.

An analysis of only the pharmacological mechanisms of a drug, although important, typically does not lead to the ability to predict or understand the behavioral effects of a substance. Over the past 30 years, behavioral pharmacology, a discipline that uses techniques derived from the experimental analysis of behavior (cf. Ferster and Skinner, 1957) and pharmacology (cf. Gilman, Goodman, and Gilman, 1980), has evolved. Since the earliest studies in behavioral pharmacology (e.g., Courvoisier et al., 1953; Dews, 1955), many reports have been published on the effects of drugs on schedule-controlled responding (for reviews, see Kelleher and Morse, 1968b; McKearney and Barrett, 1978; McMillan and Leander, 1976; Sanger and Blackman, 1976a), with the result that both parent sciences have benefited from this association (cf. Branch et al., 1977; Iversen and Iversen, 1975; S. Iversen, 1980; Seiden and Dykstra, 1977).

Advances in behavioral pharmacology have demonstrated that the effects of many drugs can be modulated by (1) the schedule of reinforcement maintaining responding (i.e., FI, FR), (2) the schedule-controlled rate and temporal pattern of responding, (3) the type of environment event maintaining or suppressing responding, (4) the eliciting, reinforcing, punishing, and discriminative properties of these environmental events, and (5) the history of the animal with respect to training and previous drug administration. An understanding of the behavioral effects of drugs requires an analysis of the modulating influences of these five factors. Previous research has delineated how the behavioral effects of benzodiazepines have been altered by the five classes of factors mentioned above.

The most frequently reported modulating factor is the schedule-controlled rate and temporal pattern of responding (for review, see Dantzer, 1977). For example, a drug can result in a variety of changes in responding depending on the schedule of reinforcement and the characteristic patterns of responding engendered (cf. Dews, 1958). Evidence that the effects of the benzodiazepines are influenced by the control rate of responding has been obtained by the use of two different types of procedure. The first involves a comparison of drug effects on overall rates of responding maintained by several different schedules of reinforcement, which typically generate different rates and temporal patterns of responding. Low and moderate doses of chlordiazepoxide have been shown to increase low rates of responding maintained by schedules that specify a minimum interresponse time (IRT) necessary to produce reinforcement. Large doses of the drug also increase responding

maintained under IRT schedules (Ando, 1975; McMillan and Campbell, 1970; Richelle et al., 1962; Sanger and Blackman, 1975a, 1976b; Sanger et al., 1974).

Low overall rates of responding maintained by schedules that result in the delivery of a reinforcer for the first response that occurs after a fixed specified period of time (Fixed-Interval or FI schedules) also can be increased by benzodiazepines in a variety of species including monkeys, cats, rats, and pigeons (Bignami and Gatti, 1969; Cook and Catania, 1964; Richelle et al., 1962). However, the increases are not always proportionally as large as those observed when responding is maintained by IRT schedules and sometimes not obtained in all subjects when pigeons are studied (Bignami and Gatti, 1969; Cesare and McKearney, 1980). Increases in moderate rates of responding maintained by schedules that reinforce the first response after variable periods of time (VI) have also been observed (Ator, 1979; Canon and Lippa, 1977a; Hanson et al., 1967; Sanger and Blackman, 1975b; Wedeking, 1974).

High rates of responding maintained by schedules that result in the presentation of a reinforcer after a specified number of responses are emitted (Fixed-Ratio or FR schedules) are usually decreased by benzodiazepines in a dose-related manner (Cesare and McKearney, 1980; Cook and Catania, 1964; Katz and Barrett, 1978). However, low doses can produce increases in high rates of responding under FR schedules (Wedeking, 1969, 1974). With all schedules of reinforcement the effects of benzodiazepines are dose related. Low and moderate doses can increase or have no effect on responding as outlined above, whereas high doses usually result in decreases.

The second approach that has been used to study the rate-dependent effects of drugs involves a detailed analysis of responding under fixed-interval schedules of reinforcement. Responding under an FI schedule can be characterized as a period of little or no responding followed by a transition to a constantly accelerating rate of responding (Branch and Gollub, 1974; Dews, 1978; Ferster and Skinner, 1957). An analysis of the rate-dependent effects of a drug on responding under FI schedules is typically performed by dividing the interval into small temporal segments (bins) and averaging response rates over these successive bins. Calculated in this way, response rates are low at the start of the interval, moderate at the middle and high at the end of the interval. This type of analysis has been questioned by Branch and Gollub (1974) and may not result in an accurate account of responding under FI schedules. Nevertheless, increases in responding that are observed with benzodiazepines under FI schedules are usually confined to the beginning of the interval. Responding toward the end of the interval is typically decreased.

Control rates of responding can also be manipulated by punishment procedures (cf. Azrin and Holz, 1966). Benzodiazepines have been demonstrated to increase responding suppressed by response-dependent electric shock with pigeons, rats, and monkeys (Cook and Davidson, 1973; Dantzer, 1978; Geller et al., 1962; McMillan, 1973; Spealman, 1979; Sepinwall et al., 1978; Wuttke and Kelleher, 1970), histamine injections with squirrel monkeys (Goldberg, 1980), and pressurized air delivered to the face with squirrel monkeys (Spealman, 1979). These studies attest the fact that benzodiazepines increase low rates of responding

suppressed by a variety of response-dependent stimuli. However, the specific determinants of this effect have been questioned. Wuttke and Kelleher (1970) maintained responding with one group of pigeons under an FI 5 min schedule. Responding by another group of pigeons was maintained under an FI 5 min schedule in which every 30th response produced an electric shock. Chlordiazepoxide, diazepam and nitrazepam increased the lower overall rates of punished responding at doses that had no effect on or decreased the overall rates of unpunished responding. Wuttke and Kelleher (1970) also examined the effects of chlordiazepoxide on comparable local rates of unpunished and punished responding obtained from different successive portions of the interval. For example, local response rates at the end of the interval schedule with punishment were compared to low local rates of responding in the early portions of the interval without punishment. Chlordiazepoxide increased similar control rates selected from different segments of the FI to the same degree. These researchers suggested therefore that benzodiazepines increase low rates of responding but do not increase punished responding to a greater extent. Recent studies using more appropriate control procedures, however, have shown that chlordiazepoxide can differentially increase responding suppressed by response-dependent electric shock (Cook and Sepinwall, 1975; Jeffrey and Barrett, 1979; Tye et al., 1979). In the study reported by Jeffrey and Barrett (1979), for example, identical rates and patterns of responding were maintained by a multiple schedule containing a component with and a component without response-produced shock. In the shock component, responding was maintained by an FI schedule of food presentation and every 30th response produced an

electric shock. The first response at the end of the FI in the other component had to be a specified IRT. Chlordiazepoxide produced greater increases in the punished component. Therefore, although benzodiazepines increase low rates of responding, proportionally greater increases are observed when responding is suppressed by response-dependent electric shock presentation.

The effects of benzodiazepines on responding suppressed by presentation of response-independent stimuli have also been reported (Dantzer, 1978; Miczek, 1973; Rawlins et al., 1980). The study by Miczek (1973) examined the effects of chlordiazepoxide and diazepam on rats using conditioned suppression procedures (cf. Estes and Skinner, 1941). In his study, responding was maintained under a VI schedule of food presentation. Responding was suppressed during the presentation of a comparatively brief stimulus that terminated with response-independent food or electric shock presentation. Chlordiazepoxide and diazepam increased responding suppressed by the stimulus paired with shock, but responding suppressed by response-independent food presentation was not increased.

Under certain situations, stimuli paired with response-independent shock can increase rather than decrease the rate of operant responding (Blackman, 1967, 1968). Sanger and Blackman (1976c) studied the effects of chlordiazepoxide in rats under one of these procedures. In this study, several doses of chlordiazepoxide were shown to increase response rates under an IRT 15 sec schedule of food presentation. These doses, however, only decreased the acceleration of responding observed in the presence of a pre-shock stimulus. Therefore, the effects of benzodiazepines

on responding under the Estes-Skinner procedure depend on the stimuli used and the response rates engendered.

Differential effects of benzodiazepines on responding controlled by different consequent events have also been reported (Ator, 1979; Barrett, 1976; Barrett et al., 1977). For example, Barrett (1976) maintained responding under a multiple FI schedule of food and electric shock presentation to squirrel monkeys (cf. Kelleher and Morse, 1968a; Malagodi et al., 1978; McKearney, 1968). In the presence of one of two different stimuli the first response after 5 min resulted in the delivery of either an electric shock or a food pellet. Several doses of chlordiazepoxide increased responding maintained by food presentation but decreased responding maintained by response-dependent shock presentation. In another study (Barrett et al., 1977) responding of squirrel monkeys was maintained by multiple FI schedules of food presentation and shock termination (cf. Kelleher and Morse, 1968a). Chlordiazepoxide in this study increased responding in the food component but only decreased responding in the termination component. However, Katz and Barrett (1978) have reported that chlordiazepoxide only decreased responding maintained by FR schedules of food presentation and shock termination with squirrel monkeys. Therefore, the dependence of drug effects on the type of maintaining event (see review, by Barrett and Katz, 1981) has demonstrated that controlling events can be significant determinants of the behavioral effects of drugs, but they must be considered in conjunction with other variables including the schedule-controlling rate and pattern of responding, and the behavioral history of the organism (cf. McKearney, 1979; Morse et al., 1977).

Schedules of reinforcement have been demonstrated to result not only in schedule-controlled behaviors but also in the appearance of other behaviors that are not explicitly reinforced. These behaviors are maintained by stimuli whose reinforcing efficacy is modulated by the explicitly arranged reinforcers. Several such "schedule-induced" or "adjunctive" behaviors have been shown to be "maintained at high probability by stimuli whose reinforcing properties in the situation are derived primarily as a function of schedule parameters governing the availability of another class of reinforcers" (Falk, 1971, p. 577). Benzodiazepines are the only class of drugs so far shown to consistently increase adjunctive behavior at doses that have no effect on or decrease operant behavior (for review, see Sanger and Blackman, 1978). Chlordiazepoxide and diazepam have been shown to increase schedule-induced drinking in rats (Bacotti and Barrett, 1976; Canon and Lippa, 1977b; Hymowitz, 1981; McKearney, 1973; Sanger and Blackman, 1976d; Sanger and Corfield-Sumner, 1979), and chlordiazepoxide has been reported to increase adjunctive drinking in squirrel monkeys (Barrett and Weinberg, 1975). These two benzodiazepines have also increased schedule-induced attack in rats and pigs (Arnone and Dantzer, 1980; Miczek, 1974). However, other studies have shown that benzodiazepines can have a taming effect (cf. Dantzer, 1977). The analysis of benzodiazepine effects on schedule-induced behavior, however, is incomplete both because of the paucity of studies and inadequate analysis of dependent measures (cf. Webbe et al., 1974). Usually only one measure such as rate is reported, but the drug could affect rate, amount or conditional probability of adjunctive behavior.

Some of the effects of benzodiazepines on schedule-controlled and schedule-induced behaviors which the consequent events are food or water have been suggested to be a direct result of their effects on eating and drinking (Fratta et al., 1976; Soubrie et al., 1975). Benzodiazepines have been reported to increase food consumption in both deprived and satiated animals at doses that decrease schedule-controlled rates of responding (Bainbridge, 1968; Cooper and Francis, 1979; Cooper and Posadas-Andres, 1979), whereas the effects of these compounds on water intake have been inconsistent; some authors have reported no effect on water intake (Falk and Burnidge, 1970; Wise and Dawson, 1974) while others have reported significant increases (Knowler and Ukena, 1973; Maickel and Maloney, 1973). It is important to note, however, that behavioral effects of benzodiazepines have been demonstrated to be not simply a function of changes in the reinforcing efficacy of food and water (Johnson, 1978; Wise and Dawson, 1974). Wise and Dawson (1974), for example, reported a well designed series of experiments comparing the effects of diazepam with food and water deprivation in rats. Diazepam, unlike food deprivation, did not result in an increase in general activity. It was also reported to be more difficult to engender and maintain responding with food presentation after diazepam was injected to rats, compared to food-deprived subjects. These data support the view that the effects of benzodiazepines are not simply related to increases in deprivation (cf. Dews, 1958).

Another area of research has been concerned with the effects of benzodiazepines on discriminative control of behavior. Several studies have shown that differential performance before a drug is administered

becomes more similar after drug administration (Laties and Weiss, 1966; Laties, 1975). This convergance of behaviors following drug administration is sometimes attributed to decreases in the control of behavior by environmental stimuli (for review, see Thompson, 1978). However, in many laboratory experiments, stimulus control is established by training subjects to respond differentially in the presence of different stimulus conditions. This can result in behavior occurring at high rates in one situation and low rates in other situations, thus confounding rate-dependent and control of behaviors by environmental stimuli.(Dews, 1971). Several discrimination tasks have been developed to provide stimulu control measures that are somewhat independent of response rates. For example, Branch (1974) trained pigeons on a procedure where the number of pecks required on a center key signalled which of two side keys would result in reinforcement. Although d-amphetamine and pentobarbital resulted in different effects on center-key rates, both drugs decreased the accuracy of side-key pecks. Rosenberg and Woods (1975), using a similar procedure, analyzed the effects of pentobarbital using a signal detection procedure (cf. Green and Swets, 1966). They reported that the decreased accuracy was due to a change in sensitivity, not response bias, at low doses and both sensitivity and bias after higher doses. Benzodiazepines have been reported to disrupt performance on discrimination tasks in which effects on stimulus control can be separated from "rate-dependent" effects in rats (Francis and Cooper, 1979; Iwasaki et al., 1976; Sahgal and Iversen, 1980), pigeons (Barthalmus et al., 1978; Sahgal and Iversen, 1978; Thompson, 1975; Tye et al., 1977), and humans (Liljequist et al., 1979).

Several studies have investigated a successive discrimination task. Sahgal and Iversen (1978) reported chlordiazepoxide disrupted performance on a conditional discrimination task in pigeons. In this study, responses to side keys were reinforced depending on whether two successive center-key stimuli were the same or different. Chlordiazepoxide (8 and 16 mg/kg) was shown to decrease accuracy and increase the latency of correct responses. The effects of chlordiazepoxide and flurazepam have been reported on a chained FI, matching-to-sample procedure in pigeons (Tye et al., 1977). Specifically, the first response on a center key after 10 sec changed the color of that key. A peck on the side key that was then the same hue as the center key sometimes resulted in food presentation. Chlordiazepoxide (20 mg/kg) was shown to increase overall response rates slightly under the FI 10 sec schedule, increase the number of center-key responses during the terminal component, and not change accuracy of side-key pecks.

In the studies described so far, benzodiazepines were administered acutely in that drug administrations have been separated by at least three days. The behavioral and pharmacological effects of many pharmacological agents have been shown to be diminished by repeated drug administrations (tolerance) (for reviews, see Corfield-Sumner and Stolerman, 1978; Krasnegor, 1977). Acute benzodiazepine injections have been shown to produce some degree of tolerance in monkeys (Cook and Sepinwall, 1975; Sepinwall et al., 1978) and rats (Ator, 1979). The daily administration of several benzodiazepines has been shown to produce tolerance to some of the behavioral effects as well as to neurochemical effects of these drugs and also to decrease their duration

of action (Goldberg et al., 1967). Tolerance to the rate-decreasing effects of chlordiazepoxide on responding under FI schedules with pigeons (Cesare and McKearney, 1980), rats (Richelle and Djahanguiri, 1964), and monkeys (Sepinwall et al., 1978) has been reported to develop after as few as four daily injections. Tolerance has also been observed in pigeons responding under a fixed-ratio schedule of food presentation (Cesare and McKearney, 1980).

Two studies have reported the effects of the chronic administration of benzodiazepines on multiple schedules in which responding was punished by response-dependent electric shock in one component. Responding in the other component was maintained by a schedule of food presentation without shock (Margules and Stein, 1968; McMillan and Leander, 1978). In both of these studies tolerance developed to the effects of the drug in the component in which responding did not produce electric shock. However, tolerance was not observed to the response rate increases produced in the component in which shock was delivered. The absence of tolerance has been reported with other effects of benzodiazepines including increased eating in rats (Wise and Dawson, 1974), dogs (Randall et al., 1960), and humans (Warner, 1965) or increased locomotive behavior in rats (Richelle and Djahanguiri, 1964) and mice (Sansone, 1979).

Some of the results of the chronic studies just described are consistent with the reinforcement "response cost" theory of the development of tolerance (Schuster et al., 1966). This theory suggests that tolerance will occur when the initial effect of the drug decreases the frequency of reinforcement. However, several exceptions to this

"rate-dependent" hypothesis have been reported (cf. Corfield-Sumner and Stolerman, 1978; Ferraro, 1977; McMillan and Leander, 1978). For example, in a study by McMillan and Leander (1978) tolerance was observed to chlordiazepoxide-induced increases in responding with rats under a fixed-interval 100 sec schedule of food presentation. However, the initial increase did not decrease frequency of reinforcement. The increasing number of exceptions reported to the response-cost notion of tolerance has led to the suggestion of a more general theory of the development of tolerance (Branch et al., 1980; Dworkin and Branch, Note 1). This theory suggests that the initial sensitivity of behavior to modification by a drug can be used as a predictor of the selective development of tolerance. Measures of behavior which show the most sensitivity to an effect of a drug should, therefore, take longer to reveal tolerance. In other words, there should be a negative correlation with respect to the initial sensitivity of a measure and the development of tolerance with that measure.

CHAPTER II
INTRODUCTION

Although many behavioral effects of the benzodiazepines have been delineated during the last 20 years, most of the research on nonhumans with schedule-controlled behavior has been designed to consider only the effects of these drugs on response rates. Moreover, only a few studies have investigated the daily administration of these widely used substances even though they are clinically prescribed on a chronic basis. The present study was designed to analyze the acute, chronic and post-chronic effects of chlordiazepoxide on the accuracy and rate of responding under a multiple schedule of food presentation using a discriminated operant procedure. The effects of methocarbamol, a muscle relaxant, were also evaluated to compare the effects of two drugs which have been demonstrated to be muscle relaxants.

Procedures which provide several dependent measures of behavior allow for a more wide-ranging analysis of the behavioral effects of drugs and also allow extension of generality to more complex procedures. Conditional discrimination procedures resulted in discriminated operants which provide both rate and accuracy measures of behavior. These procedures can therefore significantly aid our understanding of how drugs can alter responding. In the present experiments a matching-to-sample procedure was used. In this procedure, a response to a "sample" stimulus is followed by the presentation of a set of comparison stimuli.

Responses to the comparison stimulus that matches the sample stimulus are considered "correct" and are intermittently followed by reinforcement. Responses to any other comparison stimulus are denoted "incorrect" responses. Several classes of drugs have been shown to affect behavior under a matching-to-sample procedure, the most commonly studied conditional discrimination. For example, pentobarbital, lysergic acid diethylamid, and chlorpromazine have all been shown to decrease the proportion of correct responses under such procedures. These decreases in response accuracy have been observed with doses that increase, decrease or have no effect on the total number of responses (Berryman et al., 1962; Berryman et al., 1964; Lanson et al., 1979; Santi, 1979). This suggests that the effects of a drug on response rate may be separated from accuracy effects. In support of this conclusion is the demonstration that pentobarbital and chlordiazepoxide can sometimes change accuracy by the induction of a response bias (cf. Francis and Cooper, 1979; Lanson et al., 1979) rather than a nonspecific change in rate. For example, Lanson et al. (1979) reported that pentobarbital decreased control of responding by the sample stimulus. Subjects in their study developed either a position or color preference after drug administration that was not evident before the drug was administered. Before drug administration the subjects' behavior was controlled by the hue of the standard stimulus. After pentobarbital was administered the color of the comparison stimuli independent of the sample stimulus controlled responding. The results reported by Lanson et al. (1979) suggest that the effects of a drug on response rates can be independent of effects on response accuracy.

In the present study, the effects of chlordiazepoxide on pigeons responding under a multiple fixed-interval fixed-ratio schedule of reinforcement was employed. The control of behavior under fixed-interval and fixed-ratio schedules has been well studied with single key pecks. Fixed-ratio schedules have been shown to selectively reinforce short IRT's. Fixed-interval schedules differ from ratio schedules in that long IRT's are differentially reinforced (cf. Dews, 1969; Morse, 1968; Zeiler, 1977). The present study also used a matching-to-sample procedure to generate measures of both accuracy and response rate on which to study the effects of chlordiazepoxide and methocarbamol.

A multiple fixed-interval fixed-ratio schedule of reinforcement was employed in the present study because these schedules can result in different rates and accuracy of matching-to-sample performance (Boren and Gollub, 1972; Clark and Sherman, 1970; Ferster, 1960; Holz, Note 2; Nelson, 1978; Nevin et al., 1963). Nelson (1978) has shown that reinforcing matching-to-sample performance under fixed-interval schedules results in a differential reinforcement of long intermatch intervals that contain several incorrect responses. Therefore, it is possible that the control of accuracy may be different under fixed-ratio and fixed-interval schedules. Furthermore, the behavioral effects of a drug may further delineate the differential control of accuracy and response rates of discriminated operants under intermittent schedules of reinforcement.

CHAPTER III
METHOD

Subjects

Two adult male, White Carneaux pigeons, purchased from Palmetto Pigeon Plant, were maintained at approximately 80% of their unrestricted feeding weights (464 g for 2122 and 454 g for 2155). Both subjects were approximately two years old at the start of the experiment. The subjects were housed in individual cages with continuous access to water and health grit except during experimental sessions. Both subjects had been exposed to several parameters of a FR schedule of food presentation and a matching-to-sample procedure under a fixed-interval schedule of food presentation. Both subjects also received injections of delta-9-tetrahydrocannabinol and chlorpromazine before serving in the experiment. The last of these drug administrations occurred at least 44 days priors to the start of the present experiment.

Apparatus

Sessions were conducted in a 30 cm wide by 31 cm long by 31 cm deep pigeon conditioning chamber, similar to that described by Ferster and Skinner (1957). Three response keys (R. Gerbrands Co.) which would be illuminated with red or white light were mounted behind 2-cm diameter circular holes in the front wall of the chamber. The keys were extended 3 mm into the interior of the chamber by 1.8-cm diameter pieces of transparent Plexiglas. The centers of the keys were 22 cm from the floor. The center key was 15.5 cm from either side wall and the left

and right keys were 7.5 cm from their respective sides. Key pecks with a static force of 0.15N, when the keys were illuminated, produced a 60-msec click of a relay mounted behind the front wall and were recorded as a response. Two 1.1W lamps also were mounted in the upper corners of the front wall. The light from these lamps was deflected by shields attached to the bottom of the lamps. White masking noise was continuously present in the room where the chamber was located. Additional masking noise and ventilation was provided by a fan mounted on the top of the chamber.

Access to a solenoid-controlled grain feeder was provided by a rectangular (6 cm by 5 cm) hole located 10.5 cm directly below the center key. When the feeder was operated, all lights in the chamber were darkened except for a 1.1W lamp that illuminated the grain. Sessions were controlled by a PDP8/f computer operating under the Super SKED, time-share software system (Snapper and Inglis, 1978). Data were recorded by the computer and a cumulative response recorder which were located in an adjacent room.

Procedure

A trial began with illumination of the center key by either a red or white light (color randomly determined from trial to trial). A response to the center key darkened the key and the two side keys were then illuminated. One was illuminated red and the other white with the location of each color varying randomly from trial to trial. Responses to the side key that was the same color as the one most recently presented on the center key were considered correct responses, and a response to the other side key an incorrect response. For example,

if at the beginning of a trial the center key was red, a response to the red side key was correct and a response to the white side key was incorrect. Correct responses resulted in a 0.1-sec presentation of the feeder light and then darkened the chamber for 0.4 sec. Incorrect responses darkened the chamber for 0.5 sec. Either outcome was followed immediately by initiation of the next trial. When two house lights were not illuminated , the first correct response after 5 min resulted in presentation of mixed grain for 4 sec (Fixed Interval or FI 5 min). When the house lights were illuminated, the fifth correct response resulted in reinforcement (Fixed Ratio or FR 5). The ratio and interval component alternated after each food presentation. Sessions were conducted seven days a week and were terminated after eight fixed-interval and fixed-ratio components or one hour, whichever occurred first. The fixed-ratio value and the time between a side-key peck and illumination of the center key (intertrial interval or ITI) were adjusted to maintain comperable accuracy levels in the two components. Early training included a "correction procedure" in which an incorrect side-key response resulted in repeated presentations of the same center and side-key hues. The different training procedures and the number of each were studied are shown in Table 1. Terminal performance was maintained on a multiple FI 5 min FR 5 schedule of reinforcement.

Drug Procedure

Chlordiazepoxide HCL (courtesy of Hoffman-La Roche), after being dissolved in a 0.9% sodium chloride solution, was injected into the right or left breast muscle 30 prior to the start of the session.

TABLE 1
List of Procedures and Number of Sessions Each Was Studied Before Chlordiazepoxide Administration

Schedule	ITI	Number of Sessions
Mult FI 5 min, FR 30	4"	21
Mult FI 5 min, FR 15	4"	74
Mult FI 5 min, FR 1	4"	2
Mult FI 5 min, FR 1	-	3
Mult FI 5 min, FR 3	-	13
Mult FI 5 min, FR 5	-	85
Mult FI 5 min, FR 5*	-	20
Mult FI 5 min, FR 5	-	129

*Correction procedure employed.

Methocarbamol (courtesy of A.H. Robbins) was studied following both oral and intramuscular administration, made 10 min prior to the start of a session. Concentrations of both drugs were varied so as to administer them in a constant volume, proportional to the weight of the animal. Solutions of both drugs were prepared immediately prior to use. Intramuscular injections were delivered in a volume of 1 ml/kg body weight. Oral administrations were delivered in a volume of 5 ml/kg body weight. Gastric intubations were made through a 15.2-cm curved stainless steel feeding tube (Popper and Sons) inserted to the level of the opening of the proventriculus. Except for the acute administration of 23.7 mg/kg, each dose of chlordiazepoxide was administered at least twice. The acute determination of 23.7 mg/kg chlordiazepoxide was studied once. Only the largest dose of methocarbamol was given twice.

Chlordiazepoxide doses are expressed as the total salt. Saline was used as the vehicle for intramuscular injections and distilled water as the solvent for oral intubations. The acute effects of both drugs were determined by separating drug administrations by a minimum seven sessions. Control data during acute administrations were obtained from sessions following administration of the appropriate vehicle and from the days that immediately preceded drug injections.

Dose-effect curves during the daily administration of a fixed dose of chlordiazepoxide (17.0 mg/kg) were also determined. Substitution of other doses of chlordiazepoxide and of the saline vehicle during the chronic series were separated by at least seven daily injections of the chronic dose.

When daily injections of chlordiazepoxide were terminated, saline was administered daily for 15 sessions. During this time 17.0 mg/kg of chlordiazepoxide was substituted for saline after the sixth and 13th session. Injections of 17.0 and 23.7 mg/kg also were made after saline injections were discontinued.

The effects of methocarbamol were investigated after 70 days had passed since the last daily injection of 17.0 mg/kg of chlordiazepoxide. The different drug procedures and number of sessions during which each were studied are shown in Table 2.

Analysis of Results

Several measures of behavior during each session were recorded and analyzed separately for both components of the multiple schedule. These measures included: (1) the total amount of time from the start of the session or from each food presentation until the first response (post-reinforcement pause), (2) number of correct responses, (3) number of incorrect responses, and (4) correct and incorrect responses recorded separately according to the color of the center key presented and the color of the side key pecked. (For example, if the center key was red, did a response occur on a left red key or right red key?) In addition, the time to complete all ratio components and a detailed analysis of correct responses and incorrect responses in successive 30-sec segments of the fixed-interval were recorded. The temporal pattern of behavior also was displayed on the cumulative recorder.

The data allowed for an analysis of the effects of the drugs on both response rates and response accuracy under the two components of the multiple schedule. Additionally, the effects of both drugs on the

TABLE 2
Order of Drug Procedures and Number of Sessions Studied

Procedure	Number of Sessions
Determination of Acute Chloridazepoxide Dose-Effect Curve	146
Chronic Chlordiazepoxide: Fixed-Daily Dose	40
Chlordiazepoxide Substitutions	57
Daily Saline Administrations	15
Determination of the Effects of Chlordiazepoxide After Chronic Administration	55
Determination of Methocarbamol Dose-Effect Curve	40

index of curvature for the FI (cf. Fry et al., 1960) were calculated from the formula provided by Katz and Dworkin (Note 3). An index of zero indicates a constant rate of responding over the FI. Positive and negative indices, respectively, indicate increasing and decreasing rates of responding over the 5-min interval. Larger values indicate more positive or negative acceleration, respectively.

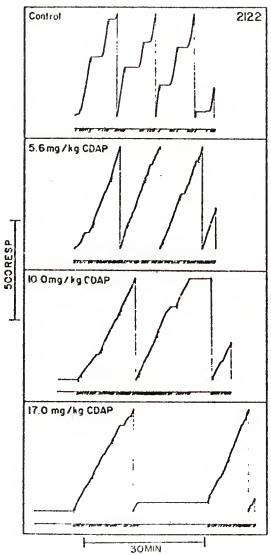
CHAPTER IV
RESULTS

Control Performance

Typical patterns of behavior occurred during each schedule component. The top panels of Figure 1 show cumulative response records of control performance under the multiple schedule for both subjects. Key pecking under the FR 5 component occurred at a high rate following a short pause after food presentation. Responding under the FI 5 min component consisted of a pause at the beginning of the interval followed by an increasing rate of responding until food delivery. Overall response rates were higher under the FR component for both subjects. Response accuracy was comparable under both schedule components for 2155 but slightly higher during the FI schedule for 2122 (see Figure 3).

The mean number of correct and incorrect responses during successive 30-sec segments of the FI are presented in Figure 2. These data were collected from sessions that directly preceded those before which an injection of chlordiazepoxide was made. Each point represents the total number of responses made in that segment during a session and is the mean from nine sessions. These graphs provide a quantitative description of temporal distribution of incorrect and correct responses during the fixed-interval. Under nondrug conditions, the average number of correct responses increased through the interval. The average number

Figure 1. Cumulative response records of control performance (top panels) and drug effects under the mult FI 5 min FR 5 schedule of matching-to-sample. The records for 2122 are displayed in the left panels and the right panels are records of responding by 2155. Y-axis: cumulative responses; X-axis: time. The response pen stopped after each key peck, and was diagonally displaced briefly after grain presentations. The event pen was deflected during the FR component and also momentarily displaced after each incorrect response.


Control
2122
5.6mg/kg CDAP
10.0mg/kg CDAP
17.0 mg/kg CDAP
500 RESP
30MIN

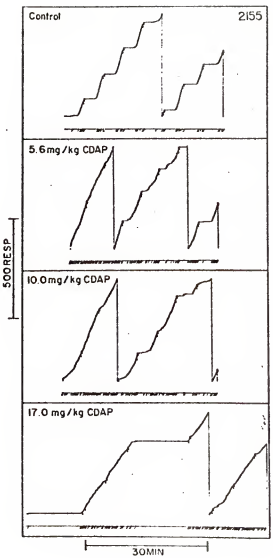
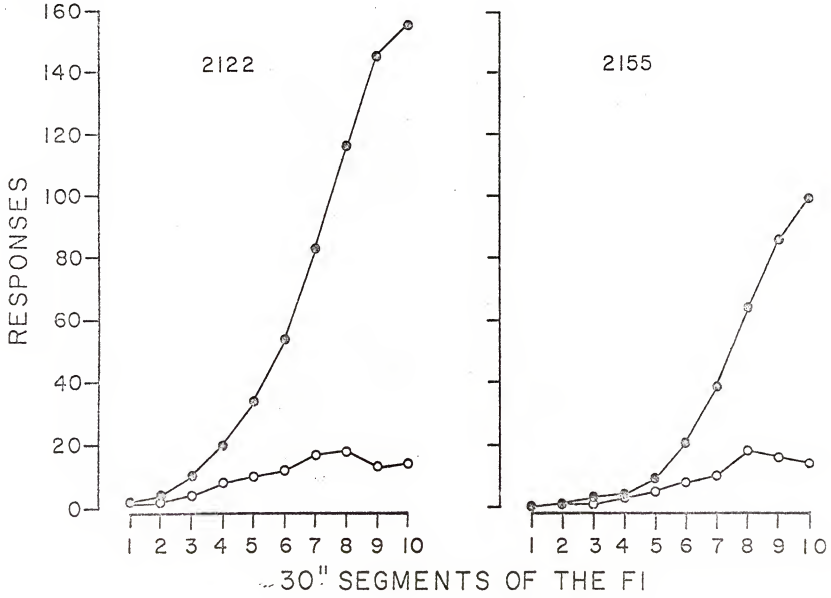

Control
2155
5.6mg/kg CDAP
10.0mg/kg CDAP
17.0 mg/kg CDAP
500 RESP
30MIN

Figure 2. Number of correct (closed circles) and incorrect (open circles) side-key responses per session during successive 30-sec segments of the FI schedule. Data are means for nine control sessions that preceded an injection of chlordiazepoxide or saline. The data for 2122 and 2155 are displayed in the left and right panels, respectively.


RESPONSES
160
140
120
100
80
60
40
20
0
2122
2155
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10
30" SEGMENTS OF THE FI

of incorrect responses increased over the first 4 min of the interval and decreased in the last min.

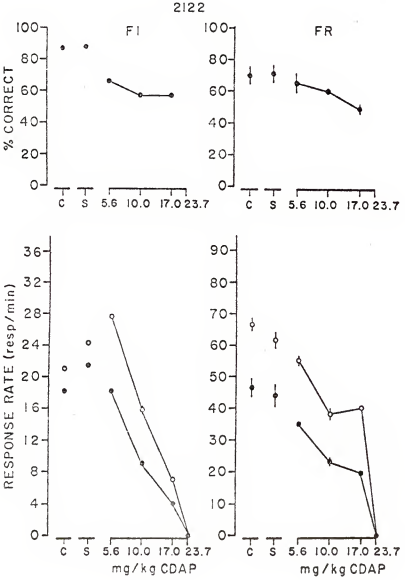
Acute Effects of Chlordiazepoxide

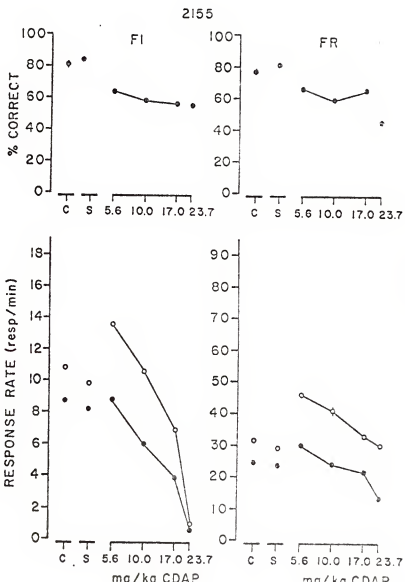
The effects of a range of doses of chlordiazepoxide (5.6 - 23.7 mg/kg) on accuracy (percent correct) and response rates (resp/min) under both schedule components are shown in Figure 3 and Figure 1. Response rates are presented for both correct side-key pecks and all side-key responses. Generally, chlordiazepoxide decreased accuracy. Every dose studied decreased response accuracy under the FI schedule for both subjects and during the FR component for 2155. Doses greater than 5.6 mg/kg decreased response accuracy under the FR component with 2122.

The lowest dose of chlordiazepoxide (5.6 mg/kg) increased overall response rates for 2155 under both schedule components and under the FI component for 2122. All response rate curves then show a decrease as a function of increasing dose of chlordiazepoxide. The injection of 17.0 and 23.7 mg/kg of chlordiazepoxide resulted in sessions being terminated by the time criterion before all possible food presentations were obtained (see bottom panels, Figure 1 above). After administration of the largest dose of the drug studied (23.7 mg/kg) 2122 did not respond during the entire session and 2155 received four food presentations before the session was terminated.

Chlordiazepoxide also produced orderly changes in the temporal patterning of responding under the FI schedule. The drug shortened or eliminated the pause at the start of the FI when responding was observed (see Figure 1 above). Moreover, the acute administration of

Figure 3. Effects of chlordiazepoxide on accuracy (percent correct top) and rates of responding (resp/min bottom), during the two schedule components for both subjects. Open symbols in the bottom panels represent overall side-key rates. Closed symbols depict the rate of correct side-key pecks. The subject and schedule component are indicated in the top of the figure. The points above "C" are means from the nine control sessions that preceded chlordiazepoxide or saline administration. Points above "S" show the effects of injecting the drug vehicle (isotonic saline). The vertical lines indicate one standard deviation (S.D.). Points without vertical lines cover 1 S.D. Unconnected points are from one session during which only a few trials were completed.


2122
FI
FR
% CORRECT
RESPONSE RATE (resp/min)
C S 5.6 10.0 17.0 23.7
mg/kg CDAP


2155
FI
FR
% CORRECT
RESPONSE RATE (resp/min)
C S 5.6 10.0 17.0 23.7
mg/kg CDAP

chlordiazepoxide resulted in dose-related decreases in the index of curvature for both subjects (see Table 3). A detailed analysis of the effects of chlordiazepoxide on the pattern of responding under the FI component is summarized in Figure 4. Several doses of the drug resulted in an increase in the low number of correct and incorrect responses at the beginning of the interval and a decrease in high numbers of corrects at the end of the interval (compare Figure 4 and Figure 2). Higher doses of chlordiazepoxide resulted in a decrease in the overall rate of both corrects and incorrects during the interval (see Figure 3), but the general nature of the disruption of the temporal pattern was unchanged.

The decreased accuracy produced by the administration of chlordiazepoxide was analyzed in more detail. Correct responses were divided into four categories depending on the color of the center and side keys. Figure 5 shows the effect of chlordiazepoxide on the four different types of correct responses in the matching-to-sample procedure. This figure allows for the identification of both color and position biases. Accuracy measures that are relatively higher in either the top or bottom quadrants for each subject indicate a position bias. A color bias is indicated by the occurrence of higher accuracy in the left or right quadrants. The points above "C" and "S" are at approximately the same value in all four quadrants. This indicates response accuracy was not a function of either a position or color bias before a dose of chlordiazepoxide was administered. A red-key bias was observed during the FI component after doses of 10.0 and 17.0 mg/kg of chlordiazepoxide were administered to 2122. This is indicated by the relatively higher

TABLE 3
The Effects of Chlordiazepoxide on the Index of Curvature During Both Acute and Chronic Administration

Dose (Mg/kg)	2122		2155	
	Acute	Chronic	Acute	Chronic
Control	.47(.06)	---	.55(.06)	---
Saline	.48(.01)	.13(.01)	.62(.05)	.21(.02)
5.6	.09(.08)	.39(.27)	.15(.13)	.40(0)
10.0	-.01(.08)	.37(.13)	.19(.06)	.53(.14)
17	-.09(.03)	.38(.06)	.01(0)	.52(.11)
23	---	.32(.23)	-.24	.63(.05)

Figure 4. Effects of chlordiazepoxide on the number of correct (closed circles) and incorrect (open circles) responses in tenths of the interval. The mean of two determinations for 5.6 mg/kg, 10.0 mg/kg and 17.0 mg/kg chlordiazepoxide are presented in the left, center, and right panels, respectively. Data from 2122 are displayed in the top of the figure. Data from 2155 are displayed in the bottom.

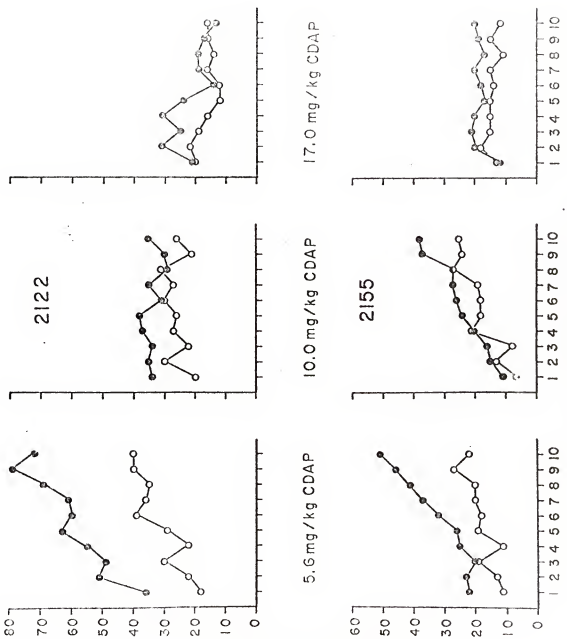
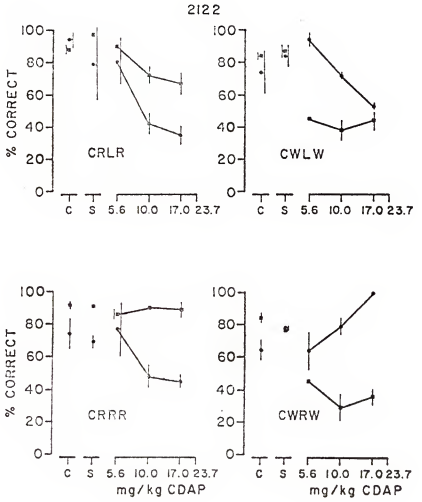
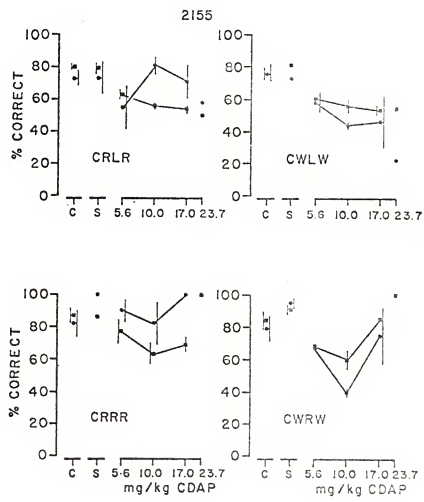

2122
2155
5.6mg/kg CDAP
10.0 mg/kg CDAP
17.0 mg/kg CDAP
RESPONSES PER SESSION
30" SEGMENTS OF THE FI
0
10
20
30
40
50
60
70
80
1 2 3 4 5 6 7 8 9 10

Figure 5. Effects of chlordiazepoxide on accuracy under both schedule components. Circles represent data during the ratio component and squares depict data from the interval component. CRLR and CRRR indicate accuracy when the center key was red and a response to the left and right key, respectively, was "correct." CWLW and CWRW indicate the data collected when the center key was white and either the left or right key was white, respectively. The bars indicate 1 S.D.


2122
% CORRECT
CRLR
CWLW
CRRR
CWRW
C S 5.6 10.0 17.0 23.7
mg/kg CDAP


2155
% CORRECT
CRLR
CWLW
CRRR
CWRW
C S 5.6 10.0 17.0 23.7
mg/kg CDAP

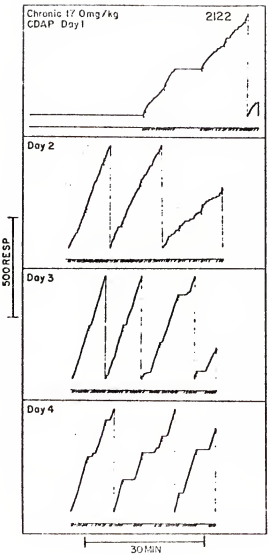
accuracy on the left quadrants of this figure. After 17.0 mg/kg of chlordiazepoxide, a bias for the right key when illuminated white occurred under the ratio contingency. Accuracy was greater than 90% correct in only the bottom right quadrant after this dose of chlordiazepoxide. In all other quadrants accuracy was below 60% correct. The administration of 17.0 mg/kg of chlordiazepoxide resulted in the same type of bias for 2155 but in the opposite schedule components. The red-key bias was observed during the ratio component, and during the interval component the color and position bias occurred.

Effects of the Daily Injection of 17.0 Mg/Kg

Figure 6 shows the cumulative records from the initial four sessions during the daily administration of 17.0 mg/kg chlordiazepoxide. Performance on the first day of chronic administration was very similar to that seen during the acute series (see Figure 1, bottom). By the second day, however, responding resembled performance observed after a lower dose of chlordiazepoxide was administered during the acute phase (see Figure 1, second and third frames). Sessions were terminated after 16 food presentations and not by the time criterion after the second and all subsequent sessions during the chronic series. Response rates and temporal patterns were approaching those observed during control performance after the fourth and all subsequent consecutive injections (compare Figure 6 bottom and Figure 1 top).

Figure 7 shows the effects of the chronic administration of chlordiazepoxide on the index of curvature for the FI and response accuracy for both components. The index of curvature approached control values by the 10th daily injection. Accuracy on the other

Figure 6. Cumulative records from the first four consecutive injections during the chronic administration of 17.0 mg/kg chlordiazepoxide. Other details are the same as for Figure 1.


Chronic 17 Omg/kg
CDAP Day1
2122
Day 2
Day 3
Day 4
500 RESP
30 MIN

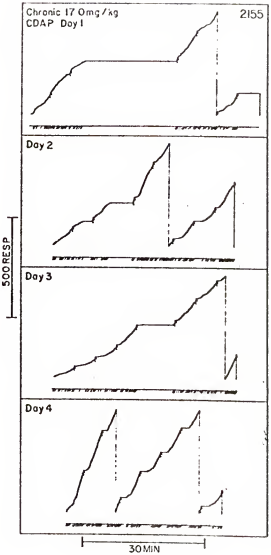
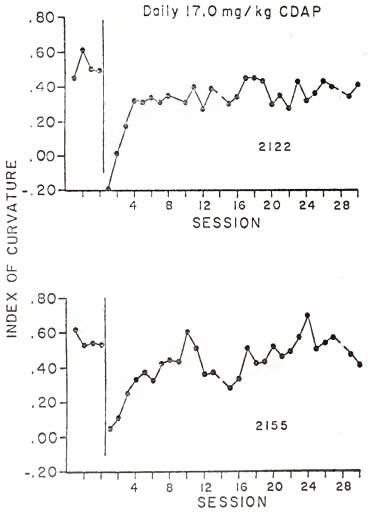
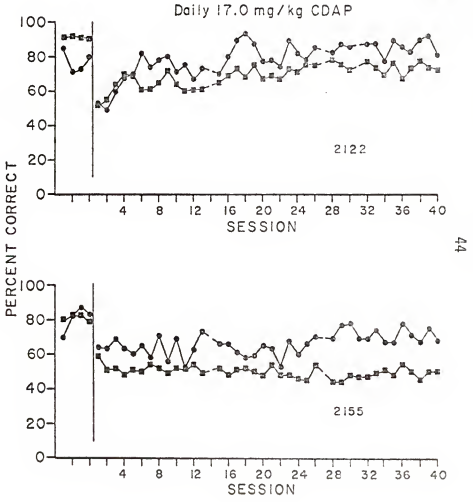

Chronic 17 Omg/kg
CDAP Day1
2155
Day 2
Day 3
Day 4
500 RESP
30 MIN

Figure 7. Daily values of index of curvature during the FI and accuracy (percent correct) during the FR (circles) and FI (squares) when 17.0 mg/kg was administered daily. The data to the left of the vertical line are from the last four sessions prior to the chronic administration of chlordiazepoxide. The absence of datum points indicate a session during which the data were not collected properly.

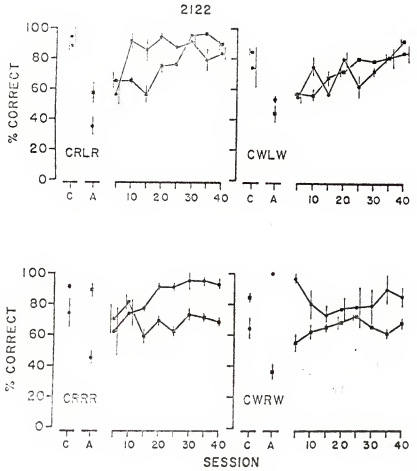

Daily 17.0 mg/kg CDAP
2122
2155
INDEX OF CURVATURE
SESSION
.80
.60
.40
.20
.00
-.20
4
8
12
16
20
24
28

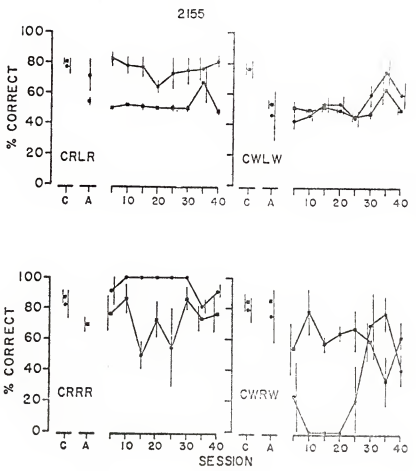

Daily 17.0 mg/kg CDAP
2122
2155
PERCENT CORRECT
SESSION
100
80
60
40
20
0
4
8
12
16
20
24
28
32
36
40

hand, returned to control levels only for 2122 under the FR component. Chlordiazepoxide continued to decrease accuracy under the FI schedule for 2122 and under both schedule components for 2155 for 40 consecutive sessions, although accuracy during the FR schedule did increase some during chronic drugging.

The effects of chlordiazepoxide on the four types of correct responses during the initial 40 days of the chronic series are summarized in Figure 8. The initial recovery of overall accuracy during the FR component for 2122 resulted from improved performance on all but the white-center key, white-right key trials. On these trials accuracy decreased. Improved performance was also observed for this subject on all trials except the red-center key, red-right key trials under the fixed-interval schedule. Responding during the FI component changed such that a red-key bias at the beginning of the chronic series was replaced by a left-key bias after 40 daily administrations. The daily administration of 17.0 mg/kg of chlordiazepoxide to 2155 initially decreased accuracy for white-center key, white-right key trials, during both schedule components. Accuracy on these trials during the ratio component, however, returned to control values after 30 daily injections. Accuracy on white-center key, white-right key trials continued to be decreased under the interval component. Accuracy levels on the three other types of trials did not change for this subject during this time under both schedule components. A red-key bias under the ratio schedule was still observed for 2155 after 40 daily administrations.

Figure 8. Accuracy (percent correct) on the four types of trials during the daily administration of chlordiazepoxide. Points above "A" are from the acute administration of 17.0 mg/kg. Datum points represent five-day means (see Figure 5). The vertical lines indicate 1 S.D. Other details for this figure are the same as Figure 5.


2122
% CORRECT
CRLR
CWLW
CRRR
CWRW
C
A
SESSION


2155
% CORRECT
CRLR
CWLW
CRRR
CWRW
C
A
SESSION

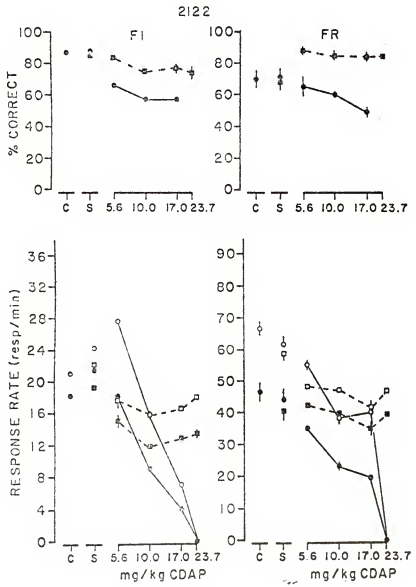
Dose Effects of Chlordiazepoxide and Saline During Chronic Chlordiazepoxide Administration

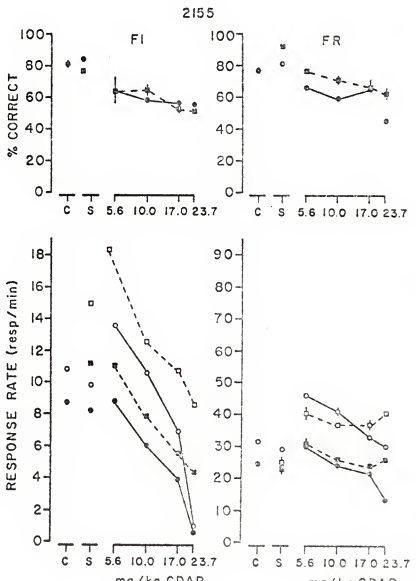
The effects of chronic administration were also examined by determining the effects of doses other than the one given chronically. Figure 9 shows the effects of substituting other doses of chlordiazepoxide for the maintenance dose of 17.0 mg/kg. The dose-effect curves for response rates were shifted to the right, as compared to the acute curves, for both subjects.

The accuracy dose-effect curves, however, were shifted to the right for 2122 only. Substituted doses of chlordiazepoxide also resulted in flat dose-effect curves for 2122 on both rate and accuracy measures. Vehicle administrations during this phase resulted in higher rates of responding than those observed before the chronic series for both subjects. The effects of both the acute and chronic administration on the index of curvature are presented in Table 3. The control values are the means from nine sessions that preceded the administration of an acute dose. All drug values except those for chronic 17.0 mg/kg are means from two determinations. The data for chronic 17.0 mg/kg are from eight sessions that directly preceded a substitution. Values in parentheses are ±1 S.D.

Substituted doses of chlordiazepoxide did not significantly change the index of curvature. However, relatively large decreases were observed when saline was substituted for the fixed-daily dose. The effects of saline on the index of curvature during the chronic administration of chlordiazepoxide were similar to those observed after 5.6 mg/kg (for 2122) and 10.0 mg/kg (for 2155) studied acutely.

Figure 9. Effects of chlordiazepoxide on overall response rates (bottom) and correct rates (bottom) and accuracy (top) during acute drug administration (filled and open circles) or during daily administration of 17.0 mg/kg chlordiazepoxide (filled and open squares). During daily drugging dose effects were determined by substituting other doses for the usual amount. Other details of the figure are the same as for Figure 3. The solid lines connect points obtained during the acute administration of chlordiazepoxide. Dashed lines connect points observed during the daily administration of chlordiazepoxide. Open symbols in the lower panels show overall rates. Filled symbols illustrate correct-response rates.


2122
FI
FR
% CORRECT
RESPONSE RATE (resp/min)
C S 5.6 10.0 17.0 23.7
mg/kg CDAP


2155
FI
FR
% CORRECT
RESPONSE RATE (resp/min)
C S 5.6 10.0 17.0 23.7
mg/kg CDAP

Post-Chronic Effects of Chlordiazepoxide

Termination of the daily injections of chlordiazepoxide resulted initially in effects similar to those observed when saline was administered during the chronic series (see Figure 9), i.e., rates were increased. The increase in response rates were not observed after the seventh saline administration. Table 4 shows the effects of several administrations of chlordiazepoxide injected up to 71 days after the chronic series was discontinued. In this table values under "CR" represent correct response rates and values under "OR" indicate overall response rates. There is only a modest indication that tolerance had dissipated over this time period (compare these data to those in Figure 9). With on exception, response rates and accuracy after drug administration were within the range of values observed during the daily administration of chlordiazepoxide and outside the range of values observed during determination of acute effects. The effects of the last administration of 17.0 mg/kg chlordiazepoxide on responding under the FI component with 2155 were within the range of the acute effects. The response rate measures under the FI schedule tended to be lower over successive administrations of chlordiazepoxide during the post-chronic period. The index of curvature (IC) was the first measure to indicate any loss of tolerance. Some effects of this dose were becoming similar to those observed during the acute administration of chlordiazepoxide.

Acute Effects of Methocarbamol

The effects of the acute administration of methocarbamol on response rates (resp/min) and response accuracy (percent correct) under the multiple FI 5 min FR 5 schedule for both subjects are shown in

TABLE 4
Post-Chronic Effects of Chlordiazepoxide on Response Rates (Resp/Min) and Accuracy (% Correct)

			FI				FR		
Subject	Session	Dose	IC	CR	OR	%C	CR	OR	%C
2122	8	17.0 mg/kg	.20	24.37	29.78	82	43.24	50.81	85
	15	"	.27	17.33	20.60	84	37.21	43.72	85
	22	"	.34	23.13	27.90	83	55.17	62.07	89
	29	"	.26	21.37	26.04	82	40.34	47.39	85
	57	"	.22	11.38	14.27	80	37.80	50.08	75
	71	23.7 mg/kg	.25	19.13	24.87	77	30.38	42.53	71
2155	8	17.0 mg/kg	.31	8.70	15.82	55	17.71	23.47	75
	15	"	.34	11.36	20.24	56	15.74	24.71	63
	22	"	.42	8.07	15.97	50	28.57	34.29	83
	29	"	.50	7.68	14.04	55	15.79	31.58	50
	57	"	.09	1.78	3.40	52	17.07	23.41	73
	71	23.7 mg/kg	.22	4.95	8.62	58	22.02	34.13	65

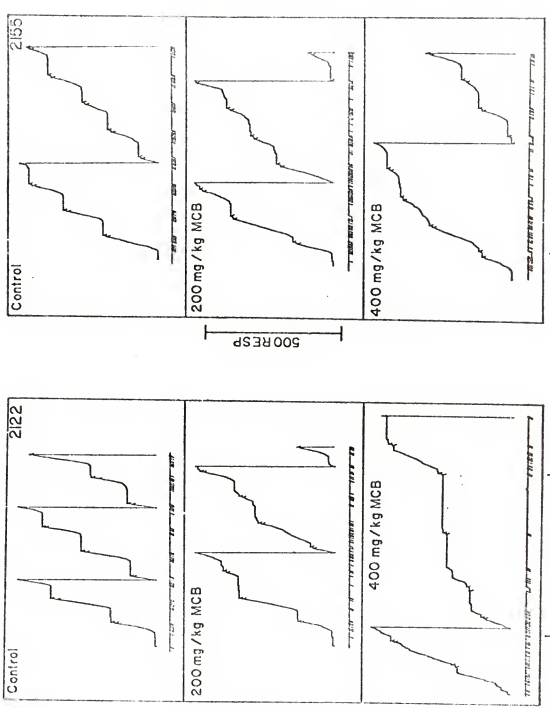
Table 5. Control values are means from session that preceded drug or vehicle administration. Other details are the same as for Table 4. Methocarbamol resulted in dose-related decreases of the rate measures. A decrease in the index of curvature was also seen after 400 mg/kg methocarbamol was administered to 2122. This drug, however, did not change accuracy at doses that decreased response rates. Figure 10 shows that the largest dose of methocarbamol, as had chlordiazepoxide, severely disrupted the temporal patterns of responding under the FI schedule. This figure also shows that the administration of methocarbamol sometimes produced a pause before responding in the ratio component, an effect rarely seen with chlordiazepoxide.

TABLE 5
Acute Effects of Intramuscular (IM) and Oral (PO) Administration of Methocarbamol on Response Rates (Resp/Min) and Accuracy (% Correct)

Subject	Dose	Route of Administration	FI				FR		
			IC	CR	OR	%C	CR	OR	%C
2122	Control		53 (6)	17.15 (1.96)	20.38 (2.47)	75 (6)	48.97 (7.86)	65.20 (7.65)	75 (5.91)
	Vehicle	PO	45	17.43	20.10	87	44.86	61.68	73
	50 mg/kg	IM	69	14.56	16.55	88	41.38	60.00	69
	100 mg/kg	IM	55	15.36	17.39	88	47.52	62.97	75
	200 mg/kg	IM	46	19.32	21.86	89	50.00	65.00	77
	200 mg/kg	PO	39	13.03	14.94	87	29.63	34.07	87
	400 mg/kg*	PO	11 (11)	10.17 (4.55)	12.41 (5.05)	81 (4)	15.23 (2.62)	18.19 (6.29)	75 (-)
2155	Control		60 (4)	8.04 (.84)	10.19 (1.34)	81 (4)	15.43 (2.19)	19.45 (1.99)	79 (4)
	Vehicle	PO	58	8.69	10.29	84	10.34	15.00	69
	50 mg/kg	IM	58	7.40	9.52	78	17.27	21.58	80
	100 mg/kg	IM	53	10.10	13.62	74	12.63	18.32	69
	200 mg/kg	IM	44	6.48	9.39	69	5.95	7.88	75
	200 mg/kg	PO	42	10.27	13.76	75	11.11	15.56	71
	400 mg/kg *	PO	44 (3)	8.33 (1.17)	11.02 (1.92)	76 (3)	9.78 (2.02)	12.59 (5.99)	71 (6)

*Mean of two determinations

Figure 10. Cumulative records of responding during control sessions (top panels) and sessions preceded by the oral administration of methocarbamol (second and third panels). Other details are the same as for Figure 1.


2122
Control
200 mg/kg MCB
400 mg/kg MCB
500RESP
30MIN
2155
Control
200 mg/kg MCB
400 mg/kg MCB
500RESP
30MIN

DISCUSSION
CHAPTER V

The present study indicates that concepts derived from schedule-controlled behavior using single-key pecks can be applied to situations in which a more complex response is studied. This study demonstrates that the reinforcement of a discriminated operant (matching-to-sample) under a multiple FI 5 min FR 5 schedule maintain pe-formances similar to those observed when single-key pecks are studied (cf. Ferster and Skinner, 1957). These findings are in accord with previous studies of matching-to-sample under FI (Boren and Gollub, 1972; Clark and Sherman, 1970; Nelson, 1978), FR (Nevin et al., 1963; Thomas, 1979), and multiple FI FR schedules of food presentation (Ferster, 1960; Holz, Note 2). Thus schedule-controlled patterns of responding show considerable generality.

The acute effects of chlordiazepoxide on overall response rates in the present study provide further evidence of the pervasiveness of schedule control. Chlordiazepoxide administered acutely produced effects in the present study that were comparable to those previously reported for single responses maintained under similar procedures. Low doses of chlordiazepoxide have been reported consistently to increase rates of responding under FI schedules in several species including cat, rat, and monkey (Barrett, 1976; Barrett et al., 1977; Cook and Catania, 1964; Hymowitz, 1981; Richelle and Djahanguiri, 1964; Richelle

et al., 1962). However, increases under FI schedules are not always observed with all subjects when pigeons are studied (Bignami and Gatti, 1969; Cesare and McKearney, 1980). The acute administration of chlordiazepoxide has been shown to increase responding maintained under FR schedules with rats (Wedeking, 1969, 1974) and decrease responding in squirrel monkeys and pigeons (Cook and Catania, 1964; Cesare and McKearney, 1980; Katz and Barrett, 1978).

In the study reported by Cesare and McKearney (1980), for example, chlordiazepoxide (administered in the same dose range used in the present study) decreased responding maintained under FR 60 schedule with two pigeons. Responding in a second pair of subjects was maintained under an FI 3 min schedule. Low doses of chlordiazepoxide increased responding above control values with one subject. Higher doses resulted in dose-related decreases for both subjects. In the present study, the effects of chlordiazepoxide on responding under the FI schedule were similar for both subjects, even though control rates were considerably different between subjects. Low doses increased the overall rate of responding above control values. Larger doses resulted in dose-related decreases in both the rate of correct and overall rate of key pecking.

The acute effects of chlordiazepoxide on responding under the FR schedule was different for the two subjects in the present study. Only dose-related decreases were observed with one subject (2122). Several doses of chlordiazepoxide increased overall response rates with the other subject (2155). The major difference between these two subjects was the higher rates of responding observed under both components for 2122 before drug administration. In the present study, small doses of

chlordiazepoxide increased the relatively low rates of responding maintained under the interval schedule with both subjects and the ratio schedule with 2155. Higher doses resulted in dose-related decreases. This drug also produced dose-related decreases in the high rates of responding under the FR with 2122. These effects are therefore "rate dependent" and have been observed when single key pecks are maintained under similar schedules. This suggests the behavioral effects of a drug may depend more on the schedule-controlled rate and pattern of responding than the nature of the response (cf. Dews, 1958; Kelleher and Morse, 1968).

In the present study, both chlordiazepoxide and methocarbamol disrupted temporal patterns of responding. However, only chlordiazepoxide decreased accuracy. Although both of these drugs are classified as centrally acting muscle relaxants, methocarbamol typically produces relatively little sedation (Bianchine, 1980). Therefore the decrease in accuracy produced by chlordiazepoxide under the matching-to-sample procedure may be the result of other properties of the drug.

In the study reported here, the acute administration of chlordiazepoxide changed both response rates and accuracy. Therefore, it is possible that the effect of the drug on response rates produced the decrease in accuracy indirectly. Since there was a low number of errors and a high number of correct responses in the absence of the drug, chlordiazepoxide may have changed accuracy by increasing low number of incorrect responses and decreasing high number of correct responses. In fact, the data from this study show that the low probabilities of both corrects and incorrects at the beginnings of the interval schedule

were increased after several doses of chlordiazepoxide. The higher average number of corrects that occurred at the end of the interval were decreased. These results are in agreement with many experiments that have shown the effects of a drug can depend on the control rate of responding (see reviews, by McMillan and Leander, 1977; Sanger and Blackman, 1976a; McKearney and Barrett, 1978). Thus, these data extend the rate-dependency theory to the effects of chlordiazepoxide on behavior under matching-to-sample procedures. These data also support the "rate-constancy" notion which suggests that administration of a drug results in a uniform rate of responding that is independent of the control rate (cf. Gonzales and Byrd, 1979). Other drugs including chlorpromazine, pentobarbital and delta-9-tetrahydrocannabinol have been reported to produce a rate-dependent effect on matching-to-sample under FI schedules (Holz, Note 2).

The effects of chlordiazepoxide on accuracy in the present study were not exclusively rate dependent. The accuracy decrements were also a function of the appearance of side and color preferences not found in control performance. The factors responsible for the induction of a color or position bias may be related to performance during the acquisition of matching-to-sample performance. Several researchers have reported that position and color biases appear during acquisition of discriminated operants but are eliminated with repeated exposure to the procedure (cf. Carter and Werner, 1978; Nevin et al., 1963). Thus, the effects of chlordiazepoxide on accuracy may have been related to bias that occurred during training (cf. Laties, 1975; Laties and Weiss, 1966; McKearney, 1979). Unfortunately, bias data were not collected during acquisition sessions.

However, a detailed analysis of incorrect responses suggests the acute administration of chlordiazepoxide changed the control of responding by the sample stimulus to the other features of the environmental context. A similar shift in the control of behavior has also been reported after the administration of pentobarbital (Lanson et al., 1978). Pentobarbital has also been reported to have similar effects as chlordiazepoxide on matching-to-sample performance (Holz, Note 2). In the present study, the way control shifted was different for response accuracy under the fixed-interval and fixed-ratio schedules. For example, large doses of chlordiazepoxide resulted in a red-key preference (2122) or a white-right key preference for 2155 under the fixed-interval schedule. Under the fixed-ratio contingencies, 2122 showed a white-right key preference and 2155 showed a red-key preference. These results reinforce the view that schedules of reinforcement are fundamental determinants of behavior and the behavioral effects of drugs (cf. Kelleher and Morse, 1968; Zeiler, 1977). Fixed-ratio and fixed-interval schedules not only engender different response rates and patterns of behavior but also differ in their control of response accuracy.

The chronic administration of chlordiazepoxide in the present study resulted in the rapid development of tolerance to the rate-decreasing effects of this drug. This is in agreement with studies reporting the development of tolerance to the rate-decreasing effects of chlordiazepoxide with rats, squirrel monkeys and pigeons (Cesare and McKearney, 1980; Cook and Sepinwall, 1975; McMillan and Leander, 1978; Sepinwall et al., 1978). By contrast, in the present study

tolerance to the accuracy-decreasing effects either did not develop (2155) or was observed only after more than 40 daily injections (2122).

The chronic administration of chlordiazepoxide also resulted in the elimination of the response bias observed with 2122 during the acute dose-effect administration. This shift in control of the conditional discrimination back to the center-key hue did not occur with the other subject.

The reinforcement-cost hypothesis of tolerance development proposed by Schuster et al. (1966) cannot account for all aspects of the results of the present study. This theory predicts that tolerance will develop differentially to those aspects of performance which reduce the frequency of reinforcement. If this theory is correct, tolerance should have differentially developed to the accuracy decrements under the FR schedule. Since large decreases in accuracy have minimal effects on the interreinforcement interval during the FI component but can decrease the reinforcement rate by half during the ratio, a differential development of tolerance should be observed. The development of tolerance in this study is more consistent with the suggestion of Branch et al. (1980). They suggested that the sensitivity of a measure of behavior to perturbation by a drug following acute administration can be used as a predictor for the selective development of tolerance.

All doses of chlordiazepoxide, in the present study, decreased response accuracy for both subjects in the two schedule components. The lowest dose of chlordiazepoxide (5.6 mg/kg) did not decrease correct response rates for 2122 under the FR component. This dose actually increased overall response rates with the same exception. Tolerance

differentially occurred to the rate measure, the least sensitive with respect to being decreased by the acute administration of chlordiazepoxide.

The development of tolerance to the effects of chlordiazepoxide on temporal patterning during the fixed-interval schedule was an exception to the suggestions of both Schuster et al. (1966) and Branch et al. (1980). The index of curvature was significantly decreased by all doses of chlordiazepoxide studied. This finding is in agreement with several studies that have reported the sensitivity of this dependent measure to the acute effects of chlordiazepoxide (e.g., Cesare and McKearney, 1980; Richelle and Djahanguiri, 1964; Tye et al., 1977). Tolerance rapidly developed to this sensitive measure when chlordiazepoxide was administered daily in the present study. The index of curvature was also significantly affected by the substitution of saline during the daily administration of chlordiazepoxide. This effect was also indicated in that the highest rates of responding during the study were observed when saline was given in place of the chronic dose. Furthermore, the index of curvature was also the first dependent measure to suggest that tolerance was dissipating after the daily administration of chlordiazepoxide was terminated.

Thus changes in temporal patterns of responding under fixed-interval schedules may be the result of non-specific rate-increasing effects of many variables. In support of this suggestion are the data reported by Holz (Note 2). His study demonstrated that manipulations such as changing light bulbs, dimming the stimulus lights, and feeding the subjects before the session changed the temporal pattern of responding

with a matching-to-sample procedure on a fixed-interval schedule of food presentation. The changes noted were in the same direction as those observed in the present study. The index of curvature is probably not a sensitive indicator of tolerance development or attenuation.

The present studies using pharmacological manipulation revealed several important findings concerning schedule-controlled behavior. It was demonstrated that response rate and response accuracy can be differentially affected by the acute and chronic administration of chlordiazepoxide. Performance of matching-to-sample reinforced under intermittent schedules of food presentation was also shown to be similar to schedule-controlled behavior using a less complex operant. Aspects of the operant baseline used in the present study were also shown to be differentially sensitive to the behavioral effects of two drugs, methocarbamol and chlordiazepoxide. Both of these drugs have muscle relaxant properties but only chlordiazepoxide is used as a sedative, hypnotic. Therefore, the baseline used may be able to screen drugs that could be used as muscle relaxants.

Furthermore, these studies have demonstrated the tolerance to some of the behavioral effects of chlordiazepoxide develop quite rapidly. Tolerance to the rate-decreasing effects of chlordiazepoxide has also been shown to take a long time to dissipate. The effects of drugs on schedule-controlled behavior are extremely complex but the use of procedures that result in several dependent measures of behavior are needed to elucidate important variables.

LIST OF APPENDICES

APPENDIX		PAGE
A	Raw Data of Number of Correct and Incorrect Responses on Four Types of Trials.	66
B	Pause and Run Times for Both Components.	73
C	Software Program--SKED State Table	76

APPENDIX A
Raw Data of Number of Correct and Incorrect Responses
on Four Types of Trials

Data From Acute Administration of Chlordiazepoxide

2122

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Control*	182 (21)	161 (18)	175 (24)	165 (18)	173 (20)	157 (16)	161 (26)	152 (20)
	Saline	198 206	177 155	206 208	185 177	190 199	160 142	200 196	176 169
	5.6	185 220	82 141	192 228	120 114	166 218	68 136	189 211	116 98
	10.0	134 152	63 129	109 105	31 45	126 141	45 115	107 100	19 35
	17.0	48 126	52 84	46 71	32 26	45 112	43 73	45 69	30 18
	23.7	-	-	-	-	-	-	-	-
Incorrect	Control	24 (12)	31 (9)	20 (8)	38 (15)	24 (12)	29 (10)	14 (7)	23 (14)
	Saline	20 6	20 32	20 28	54 54	7 6	14 31	18 21	52 51
	5.6	33 21	85 171	41 39	140 135	21 21	83 171	41 24	139 49
	10.0	50 88	117 142	14 16	94 54	33 77	109 137	11 12	92 50
	17.0	42 55	49 137	11 7	40 44	34 36	40 128	10 4	40 44
	23.7	-	-	-	-	-	-	-	-

*Numbers in parentheses indicate ±1 S.D. Numbers without parentheses represent data from each determination.

LR = left red RR = right red
LW = left white RW = right white

Data from Acute Administration of Chlordiazepoxide

2155

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Control	100 (15)	102 (16)	71 (28)	77 (13)	89 (15)	90 (15)	72 (11)	69 (14)
	Saline	87 97	104 107	71 76	73 87	77 84	92 97	62 68	64 78
	5.6	108 146	109 141	50 77	48 57	86 142	97 127	44 61	48 51
	10.0	92 110	114 92	75 38	55 19	77 94	106 78	43 31	50 16
	17.0	97 84	113 66	15 28	28 22	87 65	92 651	13 15	26 19
	23.7	22	17	2	3	15	15	1	3
Incorrect	Control	29 (10)	35 (11)	14 (10)	16 (10)	25 (10)	31 (11)	12 (11)	19 (10)
	Saline	34 19	22 25	11 10	3 13	27 17	20 18	11 10	3 12
	5.6	69 78	79 92	23 13	23 28	61 71	66 85	23 9	23 25
	10.0	78 65	75 96	55 12	45 19	76 59	64 79	38 12	24 15
	17.0	93 52	80 84	8 5	5 6	85 49	70 67	8 5	5 3
	23.7	20	20	-	-	15	13	-	-

Data From Chronic Administration of Chlordiazepoxide

2122

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Saline	145	133	177	176	138	119	173	161
		214	146	202	201	202	131	200	190
	5.6	177	125	210	197	167	114	201	187
		86	70	124	109	72	59	119	99
	10.0	109	105	164	133	96	93	155	127
		83	94	110	135	72	82	102	126
	17.0	115	100	146	150	92	89	138	141
		(24)	(18)	(17)	(13)	(15)	(20)	(17)	(14)
	23.7	63	52	152	143	53	40	143	134
		127	126	187	176	117	117	178	164
Incorrect	Saline	23	8	38	52	9	7	28	51
		12	17	26	68	4	15	24	68
	5.6	19	12	44	67	16	12	41	66
		6	6	28	52	4	5	27	52
	10.0	8	13	67	71	5	10	67	71
		17	4	60	62	13	3	56	62
	17.0	12	15	55	64	9	12	54	56
		(4)	(11)	(21)	(17)	(4)	(11)	(21)	(25)
	23.7	3	12	60	109	1	9	60	106
		13	12	54	77	10	8	54	77

Data from Chronic Administration of Chlordiazepoxide

2155

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Saline	117	121	64	84	105	114	50	77
		120	137	114	150	107	130	104	140
	5.6	170	201	13	29	156	195	4	18
		101	137	101	129	89	125	94	120
	10.0	161	151	15	47	149	142	7	36
		92	90	55	62	82	74	48	55
	17.0	106	113	17	19	92	105	8	10
		(27)	(33)	(6)	(9)	(25)	(32)	(6)	(9)
	23.7	102	90	14	12	85	84	6	3
		82	82	20	27	70	76	10	15
Incorrect	Saline	53	28	17	8	52	27	16	8
		68	27	63	19	66	26	63	18
	5.6	190	162	5	4	184	159	3	2
		55	36	37	30	50	32	37	27
	10.0	126	112	13	5	123	105	10	3
		51	52	16	12	43	46	16	7
	17.0	104	106	5	10	98	100	3	4
		(31)	(35)	(2)	(5)	(31)	(37)	(3)	(3)
	23.7	106	98	2	11	95	92	1	1
		79	74	7	8	72	70	4	4

Data From Acute Administration of Methocarbamol

2122

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Control	164 (7)	147 (11)	178 (26)	157 (8)	150 (7)	138 (11)	169 (24)	149 (9)
	Saline	214	148	209	174	197	145	195	168
	200	140	104	151	117	131	93	139	109
	400	152 131	116 119	136 65	155 74	142 120	105 100	128 62	144 67
Incorrect	Control	15 (4)	33 (11)	31 (12)	54 (23)	13 (3)	27 (10)	30 (12)	52 (20)
	Saline	12	54	15	41	10	46	13	38
	200	14	26	7	27	10	24	7	27
	400	19 48	44 40	8 11	42 11	9 43	43 34	6 9	42 11

Data From Acute Administration of Methocarbamol

2155

Response	Dose (Mg/Kg)	Total				FI			
		LR	LW	RR	RW	LR	LW	RR	RW
Correct	Control	98 (12)	108 (10)	78 (27)	85 (9)	87 (15)	95 (8)	71 (25)	75 (8)
	Saline	104	91	87	87	93	78	77	81
	200	157	131	76	55	147	119	65	48
	400	104 82	91 74	87 94	87 77	93 73	78 66	77 80	81 68
Incorrect	Control	30 (18)	32 (10)	8 (9)	8 (3)	26 (15)	28 (10)	6 (8)	7 (3)
	Saline	22	34	9	14	18	25	7	11
	200	61	79	4	1	52	76	0	1
	400	22 14	34 30	9 15	14 35	18 13	25 23	7 13	11 32

APPENDIX B
Pause and Run Times for Both Components

Data From Chlordiazepoxide Administration

Drug Regimen	Dose (Mg/Kg)	2122				2155			
		FI		FR		FI		FR	
		Pause	Run	Pause	Run	Pause	Run	Pause	Run
Acute	Control*	674 (172)	1729 (171)	9 (2)	73 (14)	989 (107)	1385 (148)	26 (15)	104 (11)
	Saline	504 601	1906 1803	21 11	86 64	651 231	1817 2181	42 30	109 80
	5.6	37 175	2388 2232	12 11	81 98	738 270	1752 2147	17 8	97 99
	10.0	331 87	2361 2357	21 17	141 105	258 624	2161 2211	13 22	114 119
	17.0	2662 629	848 2778	6 16	60 117	94 179	3320 2344	21 21	106 119
	23.7	-	-	-	-	1865	1665	7	48
Chronic	Saline	504 601	1906 1803	21 11	86 64	651 231	1817 2181	42 30	109 80
	5.6	538 896	1866 1510	14 18	65 63	544 672	1866 1731	14 31	81 85
	10.0	923 1114	1485 1289	11 17	69 72	807 1055	1608 1363	21 26	90 105
	17.0	822 (116)	1587 (116)	29 (31)	70 (6)	1191 (163)	1257 (159)	24 (8)	108 (17)
	23.7	1022 733	1389 1669	15 12	71 71	1544 1200	871 1242	20 23	109 97

*Numbers in parentheses indicate ±1 S.D. Entries without parentheses depict data from each determination.

Pause = time from start of session or food presentation until first center-key response

Run = time from first center-key response until food presentation

Data from Methocarbamol Administration

Drug Regimen	Dose (Mg/Kg)	2122				2155			
		FI		FR		FI		FR	
		Pause	Run	Pause	Run	Pause	Run	Pause	Run
Acute	Control	609 (239)	1795 (237)	12 (3)	62 (4)	1101 (199)	1304 (198)	59 (12)	131 (11)
	200	242	2160	40	64	700	1715	70	174
	400	163 169	2432 2994	177 85	81 82	1094 868	1312 1541	81 173	180 141

APPENDIX C
Software Program--SKED State Table

```
// MTS PROGRAM MULT FI 5' FR5                    9/20/78
/ .50" ITI
/       ONS
/ ON 1 - FDBK , STEP
/ ON 2 - PIP
/ ON 3 - EVENT PEN
/ ON 4 - CUM REC
/ ON 5 - LEFT KEY RED
/ ON 6 - LEFT KEY WHITE
/ ON 7 - RIGHT KEY RED
/ ON 8 - RIGHT KEY WHITE
/ ON 9 - CTR KEY RED
/ ON 10 - CTR KEY WHITE
/ ON 11 - HOUSE LIGHT
/ ON 12 - FEEDER
/       Z PULSES
/ Z1 - CTR KEY RESP
/ Z2 - LEFT KEY RESP
/ Z3 - RIGHT KEY RESP
/ Z4 - CORRECTS
/ Z5 - INCORRECTS
/ Z6 - TIME PULSE
/ Z7 - END OF FOOD
/ Z8 - FOOD START
/ Z9 - END OF ITI
/       VARIABLES
/ A = 1 - CTR KEY RED
/ A = 2 - CTR KEY WHITE
/ B = 1 - LEFT RED RIGHT WHITE
/ B = 2 - LEFT WHITE RIGHT RED
/ D - FI VALUE CHANGE FROM DEC
/ E - FI VALUE
/ F = 1 - INTERVAL TIMED OUT
/ G - FR VALUE CHANGE FROM DEC
/ I - FR VALUE
/ H = 1 - FI COMPONENT
/ H = 2 - FR COMPONENT
/ M - CORRECTS TENTHS
/ N - INCORRECTS TENTHS
/Q - PAUSE FI
/V - PAUSE FR
/       CTRS
/ CTR 1 - CENTER KEY PECKS
/ CTR 2 - LEFT KEY PECKS
/ CTR 3 - RIGHT KEY PECKS
/ CTR 4 - CR - C RED L RED
/ CTR 5 - CR - C WHITE L WHITE
/ CTR 6 - ICR - C RED L WHITE
/ CTR 7 - ICR - C WHITE L RED
/ CTR 8 - CR - C - RED R- RED
```

```
/CTR 9 -CR C WHITE R WHITE
/CTR 10 -ICR C RED R WHITE
/CTR11 -ICR C WHITE R RED
/CTR12 -- CORRECTS FR
/CTR13 -INCORRECTS FR
/CTR14 - PAUSE TIME FI
/CTR15 - PAUSE TIME FR
/CTR16 - RUN TIME FI
/CTR17 - RUN TIME FR
/CTR18 - FI INTERVAL
/CTR19 - FR INTERVAL
/CTRS 20-29 -CORRECTS TENTHS OF INTERVAL
/CTRS 30-39 -INCORRECTS TENTHS OF INTERVAL
CTRS=60


S,S.1,
S1,
        START:OPEN:ON4--->S2
S2,
        R1:Z1:ADD1:ON1--->S3
S3,
        .06":OFF1--->S4
S4,
        R4:Z2:ADD2:ON1--->S5
        R3:Z3:ADD3:ON1--->S5
S5,
        .06":OFF1--->S6
S6,
        Z7+Z9--->S2
S,S.2,
S1,
        START:WITH P=.50:ON9:SET A=1--->S2
        :ELSE:ON10:SET A=2--->S2

S2,
        Z1:OFF9,10:WITH P=.50:ON5,8:SET B=1--->S3
          :ELSE:ON6,7:SET B=2--->S3
S3,
        Z2:IF A=1:IF B=1:IF H=1[ADD4]:ADD40:Z4:OFF5,8--->S4
          :ELSE:IF A=2:IF B=2:IF H=1[ADD5]:ADD41:Z4:OFF6,7--->S4
          :ELSE:IF A=1:IF B=2:IF H=1[ADD6]:ADD42:Z5:OFF6,7--->S4
          :ELSE:IF A=2:IF B=1:IF H=1[ADD7]:ADD43:Z5:OFF5,8--->S4
        Z3:IF A=1:IF B=2:IF H=1[ADD8]:ADD44:Z4:OFF6,7--->S4
          :ELSE:IF A=2:IF B=1:IF H=1[ADD9]:ADD45:Z4:OFF5,8--->S4
          :ELSE:IF A=1:IF B=1:IF H=1[ADD10]:ADD46:Z5:OFF5,8--->S
          :ELSE:IF A=2:IF B=2:IF H=1[ADD11]:ADD47:Z5:OFF6,7--->S
S4,
        .50":Z9--->S2
```

```
S5,
        .50':Z9:IF A=1:ON9:ADD 40--->S6
            :ELSE:ON10:ADD 41--->S6
S6,
        Z1:OFF9,10:IF B=1:ON5,8--->S3
          :ELSE:ON6,7--->S3
S.S.3,
S1,
        START:SET E=300,I=5,M=20,N=30,D=E,G=I,H=1--->S2
S2,
        1':Z6:IF Q=0:ADD14--->SX
          :ELSE:ADD16--->SX
        Z1:IF Q=0:SET Q=1--->SX
          :ELSE--->SX
        D Z6:SET F=1--->S3
        30 Z6:IF N=39--->SX
             :ELSE:ADDM,N--->SX
        Z4:ADD C(N)--->SX
        Z5:ADD C(N)--->SX
S3,
        1':Z6:IF Q=0:ADD14--->SX
          :ELSE:ADD16--->SX
        Z4:Z8:ON12,2:OFF4:ADD12--->S4
S4,
        4':Z7:ON3,4,11:OFF12,2:SET F=0,H=2,D=E,Q=0:ADD18:
          :WITH P=.50:ON9:SET A=1--->S5
          :ELSE:ON 10:SET A=2--->S5
S5,
        1':Z6:IF V=0:ADD15--->SX
          :ELSE:ADD17--->SX
        Z1:IF V=0:SET V=1--->SX
          :ELSE--->SX

         Z4:SUBZGO G:Z8:ON12,2:OFF3,4,11--->S6
        Z4:ADD12--->SX
        Z5:ADD13--->SX
S6,
        4':Z7:ON4:OFF12,2:SET H=1,G=I,M=20,N=30,V=0:ADD19:
          :WITH P=.50:ON9:SET A=1--->S2
          :ELSE:ON10:SETA=2--->S2
S.S.4,
S1,
        START--->S2
S2,
        Z4:IF G=0--->SX
          :ELSE:IF F=1--->SX
          :ELSE:ON12:OFF4,5,6,7,8--->S3
        Z5:OFF4,5,6,7,8--->S5
S3,
        .10':OFF12--->S4

*
```

```
S4,
        .40':ON4:WITH P=.50:ON9:SET A=1--->S2
            :ELSE:ON10:SET A=2--->S2

S5,
        .50':Z7:ON4:WITH P=.50:ON9:SET A=1--->S2
          :ELSE:ON10:SET A=2--->S2
S.S.5,
S1,
        START--->S2
S2,
        Z5:IF H=1:ON3--->S3
          :ELSE:OFF3--->S4
S3,
        .06':OFF3--->S2
S4,
        .06':ON3--->S2
S.S.6,
S1,
        START--->S2
S2,
        16 Z8+60'--->S3
S3,
        4':OFF1,2,3,4,5,6,7,8,9,10,11,12:FOR Q=1,1,60:
                    :WRITE C(Q),16:NEXT--->S4
S4,
        .01':CLOSE--->STOP
$
```

REFERENCE NOTES

1. Dworkin, S.I., & Branch, M.N. Schedule-controlled matching-to-sample in pigeons: Disruption of performance by chlordiazepoxide. Southeastern Psychological Association, Atlanta, Ga., 1981.

2. Holz, W.C. Rate-dependency in pigeon's conditional discriminations. Southeastern Psychological Association, Miami, Fla., 1971.

3. Katz, J.L., & Dworkin, S.I. Effects of acute and chronic d-amphetamine administration on schedule-controlled resopnding in pigeons. Unpublished manuscript, University of Maryland, 1979.

REFERENCES

Ando, K. Profile of drug effects on temporally spaced responding in rats. Pharmacology Biochemistry and Behavior, 1975, 3, 833-841.

Arnone, M., & Dantzer, R. Effects of diazepam on extinction-induced aggression in pigs. Pharmacology Biochemistry and Behavior, 1980, 13, 27-30.

Ator, N.A. Differential effects of chlordiazepoxide on comparable rates of responding maintained by food and shock avoidance. Psychopharmacology, 1979, 66, 227-231.

Azrin, W.H., & Holz, W.C. Punishment. In W.K. Honig (Ed.), Operant behavior: Areas of research and application. New York: Appleton-Century-Crofts, 1966. Pp. 380-447.

Bacotti, A.V., & Barrett, J.E. Effects of chlordiazepoxide on schedule-controlled responding and schedule-induced drinking. Pharmacology Biochemistry and Behavior, 1976, 4, 299-304.

Bainbridge, J.G. The effect of psychotropic drugs on food-reinforced behaviour and on food consumption. Psychopharmacologia, 1968, 12, 204-213.

Baldessarini, R.J. Drugs and the treatment of psychiatric disorders In A.G. Gilman, L.S. Goodman, and A. Gilman (Eds.), The pharmacological basis of therapeutics. New York: MacMillan Publishing Co., Inc., 1980. Pp. 391-447.

Barrett, J.E. Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. Journal of Pharmacology and Experimental Therapeutics, 1976, 196, 605-615.

Barrett, J.E., Dworkin, S.I., & Zuccarelli, R.R. Effects of d-amphetamine, chlordiazepoxide and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination. Pharmacology Biochemistry and Behavior, 1977, 7, 529-535.

Barrett, J.E., & Katz, J.L. Drug effects on behavior maintained by different events. In T. Thompson and P.B. Dews (Eds.), Advances in behavioral pharmacology, Vol. 3. New York: Academic Press, 1981.

Barrett, J.E., & Weinberg, E.S. Effects of chlordiazepoxide on schedule-induced water and alcohol comsumption in the squirrel monkey. Psychopharmacologia, 1975, 40, 319-328.

Berryman, R., Cumming, J.A., Nevin, J.A., & Jarvik, M.E. Effects of sodium pentobarbital on complex operant discriminations. Psychopharmacologia, 1964, 6, 388-398.

Berryman, R., Jarvik, M.E., & Nevin, J.A. Effect of pentobarbital, lysergic acid diethylamide and chlorpromazine on matching behavior in the pigeon. Psychopharmacologia, 1962, 3, 60-65.

Barthalmus, G.T., Leander,J.D., and McMillan, D.E. Combined effects of ethanol and diazepam on performance and acquisition of serial position sequences by pigeons. Psychopharmacology, 1978, 59, 101-102.

Bianchine, J.R. Drugs for Parkinson's disease; Centrally acting muscle relaxants. In A.G. Gilman, L.S. Goodman, and A. Gilman (Eds.), The pharmacological basis of therapeutics. New York: MacMillan Publishing Co., Inc., 1980. Pp. 475-493.

Bignami, G., & Gatti, G.L. Analysis of drug effects on multiple fixed ratio 33 - fixed interval 5 min in pigeons. Psychopharmacologia, 1969, 15, 310-332.

Blackman, D.E. Effects of response pacing on conditioned suppression. Quarterly Journal of Experimental Psychology, 1967, 19, 170-174.

Blackman, D.E. Conditioned suppression or facilitation as a function of the behavioral baseline. Journal of the Experimental Analysis of Behavior, 1968, 11, 53-61.

Boren, M.C.P., & Gollub, L.R. Accuracy of performance on a matching to sample procedure under interval schedules. Journal of the Experimental Analysis of Behavior, 1972, 18, 65-77.

Braestrup, C., & Nielsen, M. Benzodiazepine receptors. Arzneimittel-Forshung Drug Research, 1980, 30, 852-857.

Branch, M.N. Behavior as a stimulus: Joint effects of d-amphetamine and pentobarbital. Journal of Pharmacology and Experimental Therapeutics, 1974, 189, 33-41.

Branch, M.N., Dearing, M.E., & Lee, D.M. Acute and chronic effects of 9-tetrahydrocannabinol on complex behavior of squirrel monkeys. Psychopharmacology, 1980, 71, 247-256.

Branch, M.N., & Gollub, L.R. A detailed analysis of the effects of d-amphetamine on behavior under fixed-interval schedules. Journal of the Experimental Analysis of Behavior, 1974, 21, 519-539.

Branch, M.N., Nicholson, G., & Dworkin, S.I. Punishment specific effects of pentobarbital: Dependency on the type of punisher. Journal of the Experimental Analysis of Behavior, 1977, 28, 285-293.

Canon, J.C., & Lippa, A.S. Use of DRL in differentiation anxiolytic and neuroleptic properties of CNS drugs. Pharmacology Biochemistry and Behavior, 1977a, 6, 591-593.

Canon, J.C., & Lippa, A.S. Effects of clozapine, chlorpromazine and diazepam upon adjunctive and schedule-controlled behaviors. Pharmacology Biochemistry and Behavior, 1977b, 6, 581-587.

Carter, D.E., & Werner, T.J. Complex learning and information processing by pigeons: A critical analysis. Journal of the Experimental Analysis of Behavior, 1978, 29, 565-601.

Cesare, D.A., & McKearney, J.W. Tolerance to suppressive effects of chlordiazepoxide on operant behavior: Lack of cross tolerance to pentobarbital. Pharmacology Biochemistry and Behavior, 1980, 13, 545-548.

Clark, H.B., & Sherman, J.A. Effects of a conditioned reinforcer upon accuracy of matching-to-sample behavior in pigeons. Journal of the Experimental Analysis of Behavior, 1970, 13, 375-384.

Cook, L., & Catania, A.C. Effects of drugs on avoidance and escape behavior. Federation Proceedings, 1964, 23, 818-835.

Cook, L., & Davidson, A.B. Effects of behaviorally active drugs in a conflict punishment procedure in rats. In S. Garattini, E. Mussini and L.O. Randall (Eds.), The benzodiazepines. New York: Raven Press, 1975. Pp. 379-404.

Cook, L., & Kelleher, R.T. Drug effects on the behavior of animals. Annals of the New York Academic of Sciences, 1962, 96, 315-335.

Cook, L., & Sepinwall, J. Behavioral analysis of the effects and mechanisms of action of benzodiazepines. In E. Costa and P. Greengard (Eds.), Mechanism of action of benzodiazepines. New York: Raven Press, 1975. Pp. 1-28.

Cooper, S.J., & Francis, R.L. Effects of acute and chronic administration of chlordiazepoxide on feeding parameters using two food textures in the rat. Journal of Pharmacy and Pharmacology, 1979, 31, 743-746.

Cooper, S.J., & Posadas-Andres, A. Food and water intake in the non-deprived pigeon after chlordiazepoxide administration. Psychopharmacology, 1979, 65, 99-101.

Corfield-Sumner, P.K., & Stolerman, I.P. Behavioral tolerance. In D.E. Blackman and D.J. Sanger (Eds.), Contemporary research in behavioral pharmacology. New York: Plenum Press, 1978. Pp. 391-448.

Courvoisier, S., Fournel, J., Duerot, R.J., Kolsky, M., & Koetschet, P. Propietes pharmacodynamiques du chlorhydrate de chloro-3 (dimethyl-amino-3 propyl) -10 phenthiazine. Archives Internationales de Pharmacodynamie et de Therapie, 1953, 92, 305-361.

Dantzer, R. Behavioral effects of benzodiazepines: A review. Biochemical Reviews, 1977, 1, 71-86.

Dantzer, R. Dissociation between suppressive and facilitating effects of aversive stimuli on behavior by benzodiazepines: A review and reinterpretation. Progress in Neuro-Psychopharmacology, 1978, 2, 33-46.

Dews, P.B. Studies on behavior I: Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. Journal of Pharmacology and Experimental Therapeutics, 1955, 113, 393-401.

Dews, P.B. Modification by drugs of performance on simple schedules of positive reinforcement. Annals of the New York Academy of Sciences, 1958, 65, 268-281.

Dews, P.B. Studies on responding under fixed interval schedules of reinforcement: The effects on the pattern of responding of changes in requirements at reinforcement. Journal of the Experimental Analysis of Behavior, 1969, 12, 191-199.

Dews, P.B. Drug-behavior interactions. In J.A. Harvey (Ed.), Behavioral analysis of drug action. Glenview, Ill.: Scott, Foresman & Co., 1971. Pp. 9-43.

Dews, P.B. Studies on responding under fixed-interval schedules of reinforcement II: The scalloped pattern of the cumulative record. Journal of the Experimental Analysis of Behavior, 1978, 29, 67-75.

Estes, W.K., & Skinner, B.F. Some quantitative properties of anxiety. Journal of Experimental Psychology, 1941, 29, 390-400.

Falk, J.L. The nature and determinants of adjunctive behaviour. Physiological Behavior, 1971, 6, 577-588.

Falk, J.L., & Burnidge, G.K. Fluid intake and punishment-attenuating drugs. Physiological Behavior, 1970, 5, 199-202.

Ferraro, D.P. Behavioral tolerance to marihuana. In N.P. Krasnegor (Ed.), Behavioral tolerance: Research and treatment implications. NIDA Research Monogram, 18, 1977.

Ferster, C.B. Intermittent reinforcement of matching-to-sample in the pigeon. Journal of the Experimental Analysis of Behavior, 1960, 3, 259-272.

Ferster, C.B., & Skinner, B.F. Schedules of reinforcement. New York: Appleton-Century-Crofts, 1957.

Francis, R.L., & Cooper, S.J. Chlordiazepoxide-induced disruption of discrimination behavior: A signal detection analysis. Psychopharmacology, 1979, 63, 307-310.

Fratta, W., Mereu, G., Chessa, P., Paglietti, E., & Gessa, G.L. Benzodiazepine-induced voraciousness in cats and inhibition of amphetamine-anorexia. Life Science, 1976, 18, 1157-1166.

Geller, I., Kulak, J.T. Jr., & Seifter, J. The effects of chlordiazepoxide and chlorpromazine on a punishment discrimination. Psychopharmacologia, 1962, 3, 374-385.

Gilman, A.G., Goodman, L.S., & Gilman, A. The pharmacological basis of therapeutics. New York: MacMillan Publishing Co., 1980.

Goldberg, M.G., Manian, A.A., & Efron, D.H. A comparative study of certain pharmacologic responses following acute and chronic administrations of chlordiazepoxide. Life Sciences, 1967, 6, 481-491.

Goldberg, S.R. Histamine as a punisher in squirrel monkeys: Effects of pentobarbital, chlordiazepoxide and H_1- and H_2- receptor antagonists on behavior and cardiovascular responses. Journal of Pharmacology and Experimental Therapeutics, 1980, 214, 726-736.

Gonzales, F.A., & Byrd, L.D. Mathematics underlying rate-dependency hypothesis. Science, 1977, 195, 546-550.

Green, D.M., & Swets, J.A. Signal detection theory and psychophysics. New York: Wiley, 1966.

Griffiths, R.R., Bigelow, G.E., & Liebson, I. Human sedative self-administration effects of interingestion interval and dose. Journal of Pharmacology and Experimental Therapeutics, 1976, 197, 488-494.

Griffiths, R.R., Bieglow, G., & Liebson, I. Human drug self-administration: Double-blind comparison of pentobarbital, diazepam, chlorpromazine and placebo. Journal of Pharmacology and Experimental Therapeutics, 1979, 210, 301-310.

Griffiths, R.R., Bigelow, G.E., Liebson, I., & Kaliszek, J.E. Drug preference in humans: Double-blind choice comparison of pentobarbital, diazepam, and placebo. Journal of Pharmacology and Experimental Therapeutics, 1980, 215, 649, 661.

Hanson, H.M., Witoslawski, J.J., & Campbell, E.H. Drug effects in squirrel monkeys trained on a multiple schedule with a punishment contingency. Journal of the Experimental Analysis of Behavior, 1967, 10, 565-569.

Harvey, S.T. Hyponotics and sedatives. In A.G. Gilman, L.S. Goodman, and A. Gilman (Eds.), The pharmacological basis of therapeutics. New York: MacMillan Publishing Co., 1980. Pp. 339-375.

Hymowitz, N. Effects of diazepam on schedule-controlled and schedule-induced behavior under signalled and unsignalled shock. Journal of the Experimental Analysis of Behavior, 1981, 36, 119-132.

Iversen, L.L. The present status of benzodiazepines in psychopharmacology. Arzneimittel-Forschung Drug Research, 1980, 30, 907-910.

Iversen, S.D. Animal models of anxiety and benzodiazepine actions. Arzneimittel-Forschung Drug Research, 1980, 30, 862-868.

Iversen, S.D., & Iversen, L.L. Behavioral pharmacology. New York: Oxford University Press, 1975.

Iwasaki, S., Ezawa, K., & Kwahara, S. Differential effects of chlordiazepoxide on simultaneous and successive brightness discrimination learning in rats. Psychopharmacology, 1976, 48, 75-78.

Jeffery, D.R., & Barrett, J.E. Effects of chlordiazepoxide on comparable rates of punished and unpunished responding. Psychopharmacology, 1979, 64, 9-11.

Johnson, D.W. Effect of diazepam on food consumption in rats. Psychopharmacology, 1978, 56, 111-112.

Katz, J.L., & Barrett, J.E. Ethanol, pentobarbital, and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus shock termination schedules. Psychopharmacology, 1978, 56, 153-155.

Kelleher, R.T., & Morse, W.H. Schedules using noxious stimuli III: Responding maintained with response-produced electric shocks. Journal of the Experimental Analysis of Behavior, 1968a, 11, 819-838.

Kelleher, R.T., & Morse, W.H. Determinants of the specificity of the behavioral effects of drugs. Ergebnisse der Physiologie Biologischen Chemie und Experimentellen Pharmakologie, 1968b, 60, 1-56.

Krasnegor, N.A. Behavioral tolerance: Research and treatment implication. NIDA Research Monograph 18, 1977.

Knowler, W.C., & Ukena, T.E. The effects of chlorpomazine, pentobarbital, chlordiazepoxide and d-amphetamine on rates of licking in the rat. Journal of Pharmacology and Experimental Therapeutics. 1973, 184, 385-397.

Lader, M. The present status of the benzodiazepines in psychiatry and medicine. Arzneimittel-Forschung Drug Research, 1980, 30, 910-913.

Lanson, R.N., Eckerman, D.A., & Berryman, R. Effects of sodium pentobarbital on matching behavior in the pigeon. Pharmacology Biochemistry and Behavior, 1978, 11, 159-164.

Laties, U.G. The role of discriminative stimuli in modulating drug action. Federation Proceedings, 1975, 34, 1880-1888.

Laties, U.G., & Weiss, B. Influence of drugs on behavior controlled by internal and external stimuli. Journal of Pharmacology and Experimental Therapeutics, 1966, 152, 388-396.

Liljequist, R., Palva, E., & Linnoila, M. Effects on learning and memory of two-week treatments with chlordiazepoxide lactam, n-desmethyldiazepam, oxazepam and methyloxazepam alone and in combination with alcohol. International Pharmacopsychiatry, 1979, 14, 190-198.

Lippa, A.S., Klepner, C.A., Yunger, L., Sano, M.C., Smith, W.V., & Beer, B. Relationship between benzodiazepine receptors and experimental anxiety in rats. Pharmacology Biochemistry and Behavior, 1978, 9, 853-856.

Maickel, R.P., & Maloney, G.J. Effects of various depressant drugs on deprivation-induced water consumption. Neuropharmacology, 1973, 12, 777-782.

Malagodi, E.F., Gardner, M.L., & Palermo, G. Responding maintained under fixed-interval and fixed-time schedules of electric-shock presentation. Journal of Experimental Analysis of Behavior, 1978, 30, 271-279.

Marangos, P.J., Paul, S.M., & Goodwin, F.K. Putative endogenous ligands for the benzodiazepine receptor. Life Sciences, 1979, 25, 1093-1102.

Margules, D.L., & Stein, L. Increase of "antianxiety" activity and tolerance of behavioral depression during chronic administration of oxazepam. Psychopharmacologia, 1968, 13, 74-80.

McCarthy, K.D., & Harden, T.K. Identification of two benzodiazepine binding sites on cells cultured from rate cerebral cortex. Journal of Pharmacology and Experimental Therapeutics, 1981, 216, 183-191.

McKearney, J.W. Maintenance of responding under a fixed-interval schedule of electric-shock presentation. Science, 1968, 160, 1249-1251.

McKearney, J.W. Effects of methamphetamine and chlordiazepoxide on schedule-controlled and adjunctive licking in the rat. Psychopharmacologia, 1973, 30, 375-384.

McKearney, J.W. Interrelations among prior experience and current conditions in the determination of behavior and the behavioral effects of drugs. In T. Thompson and P.B. Dews (Eds.), Advances in behavioral pharmacology, Vol. 2. New York: Academic Press, 1979. Pp. 39-64.

McKearney, J.W., & Barrett, J.E. Schedule-controlled behavior and the effects of drugs. In D.E. Blackman and D.J. Sanger (Eds.), Contemporary research in behavioral pharmacology. New York: Plenum Press, 1978. Pp. 1-60.

McMillan, D.E. Drugs and punished responding III: Punishment intensity as a determinant of drug effect. Psychopharmacologia, 1973, 30, 61-74.

McMillan, D.E., & Campbell, R.J. Effects of d-amphetamine and chlordiazepoxide on spaced responding in pigeons. Journal of the Experimental Analysis of Behavior, 1970, 14, 177-184.

McMillan, D.E., & Leander, J.D. Effects of drugs on schedule-controlled behavior. In S.D. Glick and J. Goldfarb (Eds.), Behavioral pharmacology. St. Louis: C.V. Mosby, 1977. Pp. 85-139.

McMillan, D.E., & Leander, J.D. Chronic chlordiazepoxide and pentobarbital interactions on punished and unpunished behavior. Journal of Pharmacology and Experimental Therapeutics, 1978, 207, 515-520.

Miczek, K.A. Effects of scopolamine, amphetamine and benzodiazepines on conditioned suppression. Pharmacology Biochemistry and Behavior, 1973, 1, 401-411.

Miczek, K.A. Intraspecies aggression in rats: Effects of d-amphetamine and chlordiazepoxide. Psychopharmacologia, 1974, 39, 275-301.

Morse, W.H. Intermittent reinforcement. In W.K. Honig (Ed.), Operant behavior: Areas of research and application. New York: Appleton-Century-Crofts, 1966. Pp. 52-108.

Morse, W.H., & Kelleher, R.T. Schedules of fundamental determinants of behavior. In W.N. Schoenfeld (Ed.), The theory of reinforcement schedules. New York: Appleton-Century-Crofts, 1970. Pp. 139-185.

Morse, W.H., McKearney, J.W., & Kelleher, R.T. Control of behavior by noxious stimuli. In L.L. Iversen, S.D. Iversen, and S.H. Snyder (Eds.), Handbook of psychopharmacology, Vol. 7. New York: Plenum Press, 1977. Pp. 151-180.

Nelson, T.D. Fixed-interval matching-to-sample: Intermatching time and intermatching error runs. Journal of the Experimental Analysis of Behavior, 1978, 29, 105-113.

Nevin, J.A., Cumming, W.W., & Berryman, R. Ratio reinforcement of matching behavior. Journal of the Experimental Analysis of Behavior, 1963, 6, 149-154.

Randall, L.O., Schallek, W.S., Heise, G.A., Keith, E.F., & Bagdon, R.E. The psychosedative properties of methaminodiazepoxide. Journal of Pharmacology and Experimental Therapeutics, 1960, 129, 163-171.

Rawlins, J.N.P., Feldon, J., Salmon, J.A., Gray, J.A., & Garrud, P. The effects of chlordiazepoxide HCl administration upon punishment and conditioned suppression in the rat. Psychopharmacology, 1980, 70, 312-322.

Richell, M., & Djahanguiri, B. Effet d'un traitement prolonge au chlordiazepoxide sur un conditionnement temporel chez le rat. Psychopharmacologia, 1964, 5, 106-114.

Richelle, M.B., Xhenseval, B., Fontaine, D., & Thone, L. Action of chlordiazepoxide on two types of temporal conditioning in rats. International Journal of Neuropharmacology, 1962, 1, 381-391.

Robertson, H.A. Benzodiazepine receptors in "emotional" and "non-emotional" mice: Comparison of four strains. European Journal of Pharmacology, 1979, 56, 163-166.

Rosenberg, J., & Woods, J.H. Effects of pentobarbital on fixed-ratio discrimination. Bulletin of the Psychonomic Society, 1975, 5, 33-35.

Sahgal, A., & Iversen, S.D. The effects of chlordiazepoxide on a delyaed pair comparison task in pigeons. Psychopharmacology, 1978, 59, 57-64.

Sahgal, A., & Iversen, S.D. Recognition memory, chlordiazepoxide and rhesus monkeys: Some problems and results. Behavioral Brain Research, 1980, 1, 227-243.

Sanger, D.J., & Blackman, D.E. The effects of chlordiazepoxide on the development of adjunctive drinking in rats. Quarterly Journal of Experimental Psychology, 1975a, 27, 499-505.

Sanger, D.J., & Blackman, D.E. Rate-dependent effects of drugs on the variable interval behavior of rats. Journal of Pharmacology and Experimental Therapeutics, 1975b, 194, 343-350.

Sanger, D.J., & Blackman, D.E. Rate-dependent effects of drugs: A review of the literature. Pharmacology Biochemistry and Behavior, 1976a, 4, 73-83.

Sanger, D.J., & Blackman, D.E. Effects of chlordiazepoxide, ripazepam and d-amphetamine on timing behavior in rats. Psychopharmacology, 1976b, 48, 209-215.

Sanger, D.J., & Blackman, D.E. Schedule-dependnet effects of chlordiazepoxide on operant behavior in rats. Psychological Record, 1976c, 26, 131-134.

Sanger, D.J., & Blackman, D.E. Effects of diazepam and ripazepam on two measures of adjunctive drinking in rats. Pharmacology Biochemistry and Behavior, 1976d, 5, 139-142.

Sanger, D.J., & Blackman, D.E. The effects of drugs on adjunctive behavior. In D.E. Blackman and D.J. Sanger (Eds.), Contemporary research in behavioral pharmacology. New York: Plenum Press, 1978. Pp. 239-287.

Sanger, D.J., & Corfield-Sumner, P.K. Schedule-induced drinking and thirst: A pharmacological analysis. Pharmacology Biochemistry and Behavior, 1979, 10, 471-474.

Sanger, D.J., Key, M., and Blackman, D.E. Differential effects of chlordiazepoxide and d-amphetamine on responding maintained by a DRL schedule of reinforcement. Psychopharmacologia, 1974, 38, 159-171.

Sansone, M. Effects of repeated administration of chlordiazepoxide on spontaneous locomotor activity in mice. Psychopharmacology, 1979, 66, 109-110.

Santi, A. The effects of sodium pentobarbital on matching and oddity performance in pigeons. Animal Learning and Behavior, 1979, 2, 229-232.

Schuster, C.R., Dockens, W.S., & Woods, J.H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia, 1966, 9, 170-182.

Seiden, L.S., & Dykstra, L.A. Psychopharmacology: A biochemical and behavioral approach. New York: Van Nostrand Reinhold Co., 1977.

Sepinwall, L., Grodsky, F.S., & Cook, L. Conflict behavior in the squirrel monkey: Effects of chlordiazepoxide, diazepam and N-desmethldiazepam. Journal of Pharmacology and Experimental Therapeutics, 1978, 204, 88-102.

Snapper, A.G., & Inglis, G. The SKED software system: Timed-shared super SKED. Kalamazoo, Mich.: State Systems, Inc., 1978.

Snyder, S.H., & Childers, S.R. Opiate receptors and opioid peptides. Annual Review of Neuroscience, 1979, 2, 35-64.

Soubrie, P. Kulkarni, S., Simon, P., & Boissier, J.R. Effets des anxiolytiques sur la prise de nourriture de rats et de souris places en situation nouvelle ou familiere. Psychopharmacologia, 1975, 45, 203-210.

Spealman, R.D. Comparison of drug effects on responding punished by pressurized air or electric shock delivery in squirrel monkeys: pentobarbital, chlordiazepoxide, d-amphetamine, and cocaine. Journal of Pharmacology and Experimental Therapeutics, 1979, 209, 309-315.

Squires, R.F., & Braestrup, C. Benzodiazepines receptors in rat brain. Nature, 1977, 266, 732-734.

Thomas, J.R. Matching-to-sample accuracy on fixed-ratio schedules. Journal of the Experimental Analysis of Behavior, 1979, 32, 183-189.

Thompson, D.M. Repeated acquisition of response sequences: Stimulus control of drugs. Journal of the Experimental Analysis of Behavior, 1975, 23, 429-436.

Thompson, D.M. Stimulus control and drug effects. In D.E. Blackman and D.J. Sanger (Eds.), Contemporary research in behavioral pharmacology. New York: Plenum Press, 1978. Pp. 159-207.

Tye, N.C., Sahgal, A., & Iversen, S.D. Benzodiazepines and discrimination behavior: Dissociation of response and sensory factors. Psychopharmacology, 1977, 52, 191-194.

Tye, N.C., Iversen, S.D., & Green, A.R. The effects of benzodiazepines and serotonargic manipulation on punished responding. Neuropharmacology, 1979, 18, 689-695.

Warner, R.S. Management of the office patient with anxiety and depression. Psychosomatics, 1965, 6, 347-351.

Webbe, F.M., DeWeese, J., & Malagodi, E.F. Induced attack during multiple fixed-ratio variable-ratio schedules of reinforcement. Journal of the Experimental Analysis of Behavior, 1974, 22, 197-208.

Wedeking, P.W. Disinhibition effects of chlordiazepoxide. Psychonomic Science, 1969, 15, 232-233.

Wedeking, P.W. Schedule-dependent differences among anti-anxiety drugs. Pharmacology Biochemistry and Behavior, 1974, 2, 465-472.

Wise, R.A., & Dawson, V. Diazepam-induced eating and lever pressing for food in sated rats. Journal of Comparative and Physiological Psychology, 1974, 86, 930-941.

Wuttke, W., & Kelleher, R.T. Effects of some benzodiazepines on punished and unpunished behavior in the pigeon. Journal of Pharmacology and Experimental Therapeutics, 1970, 172, 397-405.

Zeiler, M. Schedules of reinforcement: The controlling variables. In W.K. Honig and J.E.R. Staddon (Eds.), Handbook of operant behavior. Engelwood Cliffs, N.J.: Prentice-Hall, 1977. Pp. 201-232.

BIOGRAPHICAL SKETCH

Steven Ira Dworkin was born on March 24, 1954, in Baltimore, Md. He graduated from Pikesville Senior High School in June 1972. He attended the University of Maryland in College Park, Md., where he received a Bachelor of Science degree in psychology in 1976. Mr. Dworkin then moved to Florida and entered the University of Florida's graduate program in the experimental analysis of behavior. While there he earned a Master of Science degree in 1979 and a Doctor of Philosophy degree in 1981, both in psychology. Mr. Dworkin has accepted a post-doctoral research position at the Louisiana State University Medical Center in Shreveport starting in 1981.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Marc N. Branch, Chairman
Associate Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

E.F. Malagodi
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

H.S. Pennypacker
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert J. Waldbillig
Assistant Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Steven R. Childers
Assistant Professor of Pharmacology and Therapeutics

This dissertation was submitted to the Graduate Faculty of the Department of Psychology in the College of Liberal Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 1981

Dean for Graduate Studies and Research